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ARCHIVES OF SURGERY

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INTERVERTEBRAL DISK EXTENSIONS INTO THE VERTEBRAL BODIES AND THE SPINAL CANAL*

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Intervertebral disk extensions into the adjacent vertebral bodies or into the spinal canal have until recently been unknown. Schmorl,[1] in 1926, was the first to direct attention to this pathologic condition. On removal and sagittal sectioning of the vertebral column in routine post-mortem examinations, he found one or more intervertebral disk extensions in the vertebral bodies in 38 per cent of the spines examined. Schmorl named these areas of disk invasions of the bodies cartilage nodes (Knorpel Knötchens). In 1929, both Andrae [2] and Schmorl [3] described similar disk extensions into the spinal canal.

Since Schmorl's first description of the pathologic picture of the intervertebral disk extensions into the vertebral bodies, a number of papers dealing with the clinical phase of this subject have appeared in the German literature. Schanz,[4] in a paper on the vertebral column and trauma, suggested the possibility of a direct causal relationship between the intervertebral disk extensions or cartilage nodes and symptoms in the back. Dittrich [5] and Mau [6] reported single cases of pain in the back and disability, where the lateral roentgenograms showed the

* Submitted for publication, June 21, 1930.

* The pathologic specimens were removed by the author on autopsy at the Pathologic Institute of the Stadt Krankenhaus Dresden Friedrichstadt, of which Geheimrat Prof. Schmorl is the director. The roentgenograms and clinical cases are from the roentgenologic and orthopaedic departments of the Hospital for Joint Diseases, New York.

1. Schmorl, G.: Die pathologische Anatomie der Wirbelsäule, Verhandl. d. deutsch. orthop. Gesellsch. (1926) Kong. 21, p. 3, 1927.

2. Andrae, R.: Ueber Knorpelknötchen am hinteren Ende der Wirbelbandscheiben im Bereich des Spinalkanals, Beitr. z. path. Anat. u. z. allg. Path. **82**:464 (Sept. 20) 1929.

3. Schmorl, G.: Ueber Knorpelknötchen an der Hinterfläche der Wirbelbandscheiben, Fortschr. a. d. Geb. d. Röntgenstrahlen. **40**:629, 1929.

4. Schanz, A.: Wirbelsäule und Trauma, Arch. f. klin. Chir. **148**:187, 1927.

5. Dittrich: Der röntgenologische Nachweis von Knorpelknötchen im Wirbel, Verhandl. d. deutsch. orthop. Gesellsch. (1928) Kong. 23, p. 295, 1929.

6. Mau, C.: Der röntgenologische Nachweis der traumatischen Knorpelknötchenbildung am Wirbelkörper, Zentralbl. f. Chir. **55**:386 (Feb. 18) 1928.

presence of cartilage nodes. Müller,[7] in five cases, three of which gave a history of pain in the back, found roentgen evidence of intervertebral disk extensions of one or more vertebral bodies.

The clinical significance of intervertebral disk extensions is as yet not established. Up to the present only seven clinical cases with roentgen evidences of disk extensions into the vertebral bodies have been reported in the literature. This condition is relatively unknown, and although a number of papers have been published in German, no paper has yet appeared in English.

In this paper I shall describe the pathologic picture and roentgen appearance of the intervertebral disk extensions, and I shall attempt to state their clinical significance.

ANATOMY AND PHYSIOLOGY

The intervertebral fibrocartilages or disks are interposed between adjacent vertebral bodies and form the chief bond of union between the vertebrae. They consist of an annulus fibrosus, nucleus pulposus and two thin cartilage plates.

The annulus fibrosus is a circumferential lamellar layer surrounding the nucleus pulposus. It is firm, fibrous and chemically water poor. The nucleus pulposus is situated slightly posterior to the center of the disk, commonly at the junction of the middle and posterior third of the vertebral body. It is a very elastic and tightly compressed material, which bulges out freely when the confining pressure is removed. The nucleus is expansile, soft, water rich, and has the constant tendency to spring out of its confinement in the direction of least resistance. The cartilage plates are thin layers of hyaline cartilage, which cover the proximal and distal surfaces of the bodies.

The intervertebral disks comprise from one fourth to one fifth of the entire vertebral length. They vary in size and shape with the bodies they unite. They are widest and thickest in the lumbar region. In the cervical and lumbar regions they are thicker in front than behind, giving rise to a forward convexity of the spine. In the thoracic region, the disks are flattened and have only a slight effect on the posterior convexity of the dorsal part of the spine.

The elasticity of the intervertebral disks rests in the nucleus pulposus. In the normal state it is compressed and acts as an elastic cushion, or spring. Roux [8] compared the intervertebral disks to a hydraulic press. The disks act as shock absorbers and buffers against slight traumas. They diminish the jarring effects of the vertebrae in walking, running, jumping or other movements of the spine.

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8. Roux, quoted by Schmorl: Verhandl. d. deutsch. path. Gesellsch. **22**:250, 1927.

7. Müller, Walther: Das röntgenologische Bild und die klinische Bedeutung der sogenannten Knorpelknötchen der Wirbelsäule, Beitr. z. klin. Chir. **145**:191, 1928.

The disks are in relation in front with the anterior longitudinal ligament; behind, with the posterior longitudinal ligament; proximately and distally, with the adjacent surfaces of the vertebral bodies; and laterally, in the thoracic region with the interarticular and radiate ligaments.

The intervertebral disks have normally no blood vessels. They receive their nourishment through the cartilaginous plate from the bony marrow by diffusion.

The bodies of the adjacent vertebrae are composed of cancellous tissue covered by a thin coating of compact bone, which is normally perforated by numerous small orifices. This thin plate of compact bone acts as a protecting layer of the body against the constant pressure of the disk substance. The interior of the bone is traversed by one or two large irregular canals for the exit of the basivertebral veins from the vertebral body. Over the anterior surface of the bone are several small apertures for the entrance of nutrient vessels.

DEFECTS IN THE VERTEBRAL BODIES

In a sagittal section of a normal spine at autopsy, the expansile fibers of the disks, which rest almost entirely in the nucleus pulposus, are raised above the surrounding surfaces. This highly expansile tissue is separated from the adjacent cancellous stroma of the bodies by a thin cartilage plate and a thin layer of compact bone. In a number of specimens, due to the normal physiologic tension of the disk substance, small semicircular depressions may be noted over the posterior third of the bodies around the location of the nucleus pulposus. These small "doming" defects may be seen in young persons around or shortly after the close of their growing period and represent a slight structural weakness of the vertebral bodies. The cartilage and bony plates are as a rule intact, although in some cases the cartilage plate around the depression is very thin. However, no invasion of the spongiosa usually occurs.

SCHMORL'S CARTILAGE NODES (KNORPEL KNÖTCHENS)

In a rather large number of specimens, the expansile disk fibers succeed in invading one or more vertebral bodies. The cartilage and bony plates are usually injured, and as a result, the disk substance extends into the body. The extent of the invasion of the spongiosa is small, usually not larger than a pea in area. In one or two cases, the break in the continuity of the protecting plates may be so large that part of the disk substance may virtually prolapse or herniate through the opening. It is these intervertebral disk invasions that Schmorl described and named cartilage nodes. In young persons or in a recently invaded body, the cartilage node presents a white, soft glistening appearance; later, it assumes a light blue hue, and becomes hard and cartilaginous.

The cartilage node varies in size from that of a pinhead to that of a grape, and is most frequently found over the lower thoracic and upper lumbar vertebrae (fig. 3*A*).

ETIOLOGY

The most important etiologic factor is trauma. This may be manifested in the form of mild, repeated injuries to the spine, as for example, persons doing hard manual work. This continued trauma may go on for years without causing any signs or symptoms of disability. Yet at autopsy, or in some cases in the lateral roentgenogram, small disk extensions of the bodies are found. In another group of cases, a severe sudden injury to the spine, as in a direct blow or fall on the back, may cause a break in the continuity of the protecting plates. With the establishment of an open door, the expansile disk substance invades the body spongiosa. In many of these specimens, small hemorrhages and vascular engorgements are seen around the invaded glistening disk fibers. Infrequently, a direct injury, as a gunshot or stab wound to the vertebral body extending through the bony and cartilage plate occurs, and as a result may lead to the extension of the disk substance into the spongiosa. Schmorl,[9] in an examination of the spines of 3,000 persons found the latter condition present in only 2, both of whom were war veterans.

Another factor is degenerative or arthritic changes of the cartilage plate. This occurs in a small percentage of persons, particularly in late adult life. The cartilage plate becomes hard and brittle, and under the expansile pressure of an active disk, a tear or break in continuity easily occurs. In some cases, the fibers extend through the small orifices in the bony plate and through pressure atrophy of the intervening trabeculae invade the spongiosa.

In diseased conditions of the vertebral bodies, such as osteoporosis, osteomalacia, tumor metastases or multiple myelomas, the resistance of the vertebral bodies may be considerably lowered. When the intervertebral disks are active, the expansile tension of the disks is often sufficient virtually to compress the bodies, giving them an hourglass or fish vertebrae appearance (fig. 8*A*).

PATHOLOGIC CHANGES OF THE INVADING INTERVERTEBRAL DISK SUBSTANCE

Following the extension of the disk fibers into the vertebral body, a hyperplasia of the cartilage cells of the intervertebral disk takes place, and in time, the soft, glistening, expansile invaded disk substance

9. Schmorl, G.: Ueber Knorpelknötchen an den Wirbelbandscheiben, Fortschr. a. d. Geb. d. Röntgenstrahlen **38**:265 (Aug.) 1928.

becomes hard and cartilaginous. This cartilage node develops principally from the cartilage cell hyperplasia of the intervertebral disk substance. The cartilage cells of the cartilage plates do not seem to take part. In young persons in whom the endochondral growth has not ceased, the cartilage cells from the growing cartilage layer take part. According to Schmorl,[10] the cartilage nodes are to be considered as a "cartilage callous hyperplasia."

In early cases, small hemorrhages, blood pigment and vascular engorgements of the blood vessels are found around the invaded disks.

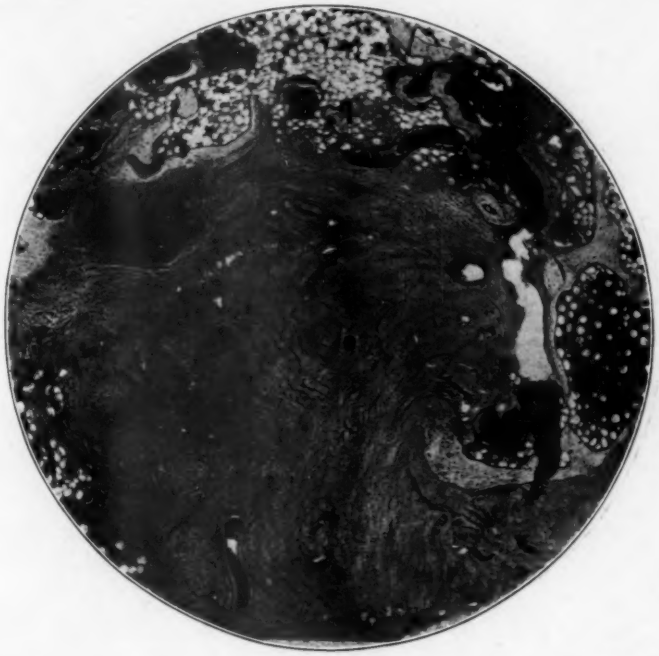

Fig. 1.—Low power photomicrograph of an intervertebral disk extension into a vertebral body. Note the marked vascular engorgement and dilatation of the vessels surrounding the disk node.

Later, vascular infiltration and new vessel formations appear (figs. 1 and 2). Around the margin of the cartilage node endochondral ossification and new bone formation set in, which may extend and involve the entire disk node (figs. 2, 4 *A* and 5 *A*). The extended intervertebral disk node may also undergo cystic degeneration (fig. 6 *A*).

10. Schmorl, G.: Ueber die an den Wirbelbandscheiben vorkommenden Ausdehnungs-und Zerreissungsvorgänge und die dadurch an ihnen und der Wirbelspongiosa hervorgerufenen Veränderungen, Verhandl. d. deutsch. path. Gesellsch. **22**:250, 1927.

FREQUENCY OF CARTILAGE NODES

Schmorl, in a review of 2,000 cases at autopsy, found cartilage nodes in 737, or 38 per cent. Of this number, 39 per cent were found in males and 34 per cent in females. For persons from 18 to 59 years of age the figures were: males, 40 per cent; females, 20 per cent; from 60 to 95 years, males, 23 per cent; females, 44 per cent. In early adult life between 18 and 29 years, Schmorl found 39 per cent in males and 18 per cent in females.

Fig. 2.—Low power photomicrograph of an intervertebral disk node and part of a vertebral body. Note the thick bony barrier at the upper end, and the marked vascular infiltration and engorgement at the left.

INTERVERTEBRAL DISK EXTENSIONS INTO THE SPINAL CANAL

Andrae,[2] in an examination of 368 vertebral columns at autopsy, found intervertebral disk extensions into the spinal canal in 56, or 15.2 per cent. These posterior disk extensions are analogous to the cartilage nodes described by Schmorl. They appear as small, firm, pea-sized projections of disk substance on the anterior surface of the spinal canal. Schmorl[3] found in a woman of 49, a bony hard, bean-shaped extension of the tenth intervertebral disk, which projected 4 mm. into the spinal canal, and which caused a lateral displacement of the cord. Von

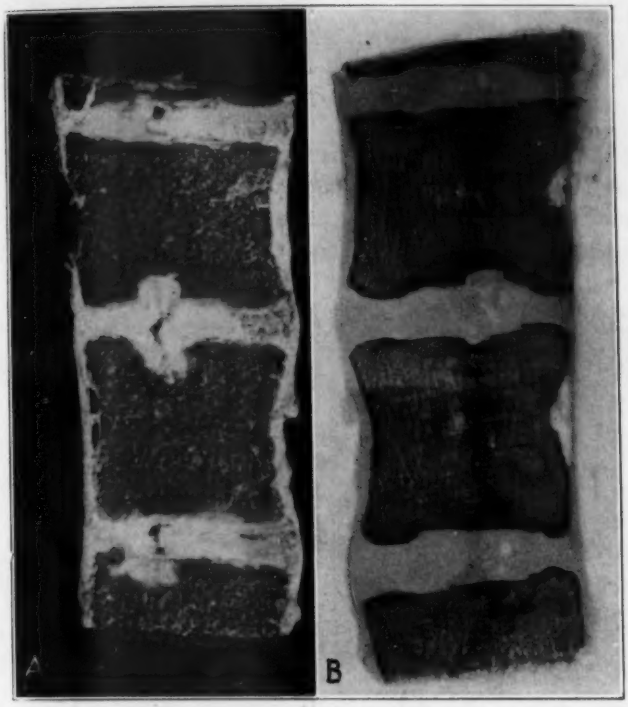

Fig. 3.—*A* shows a sagittal section of several vertebral bodies with three disk extensions. The upper two nodes have a soft elastic consistency, the lower one is cartilaginous and in places ossified. *B* is a roentgenogram of section *A*. The upper disk node presents a bony defect or area of bone destruction, the lower node presents bone production.

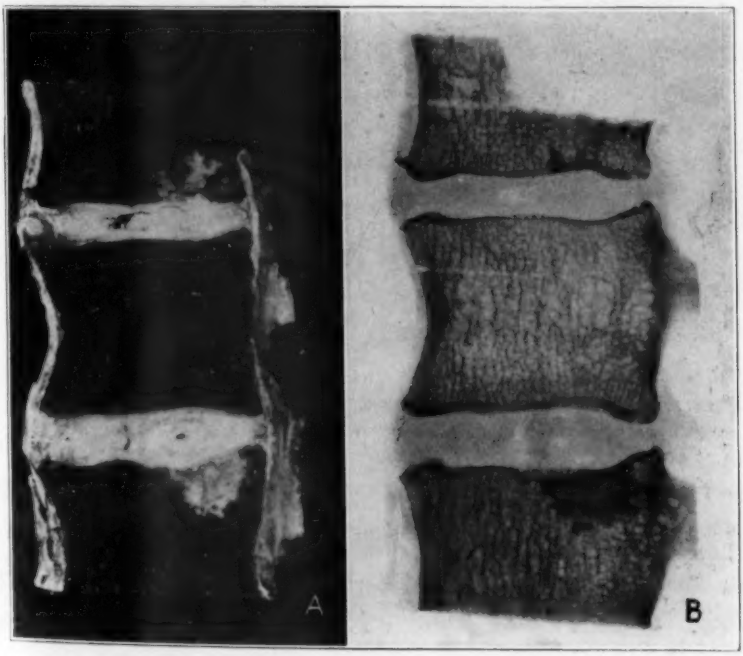

Fig. 4.—*A* shows two calcified disk nodes. *B* is a roentgenogram of *A*. Note the irregular dense shadow of the lower node.

Pechy [11] found in a man of 49, a hard, bean-sized growth of the seventh thoracic intervertebral disk substance in the spinal canal, which produced a backward displacement of the cord. Andrae [2] and Schmorl [3] were of the opinion that this benign growth is an intervertebral disk

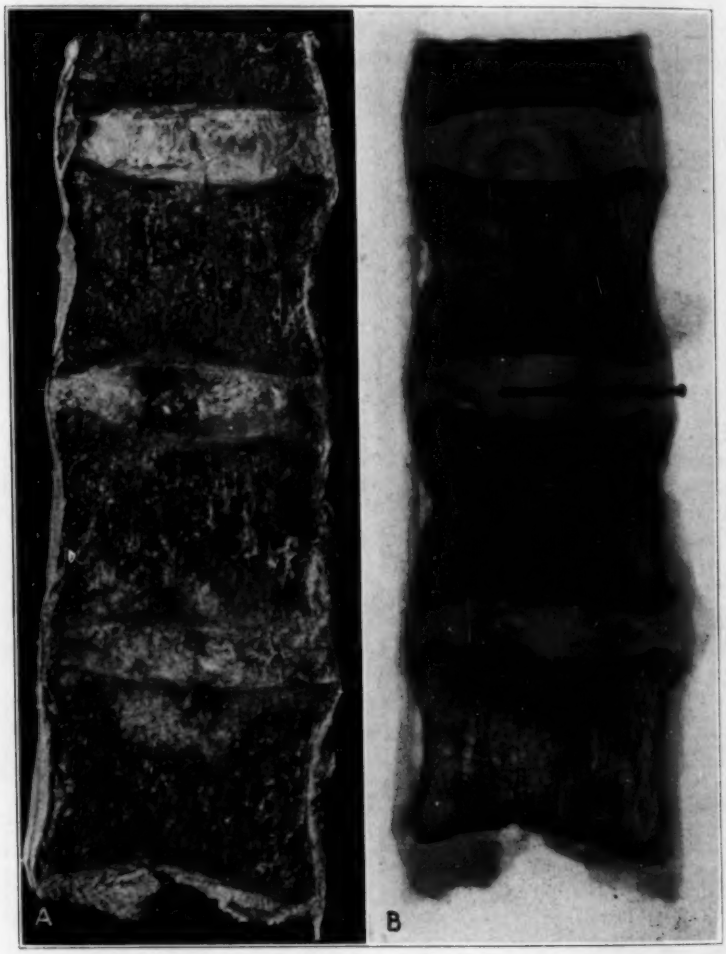

Fig. 5.—*A* shows a sagittal section of the spine with two degenerated disk nodes surrounded by dense compact bone. *B* is a roentgenogram of section *A*. Note the areas of lessened density surrounded by dense sclerotic bone.

node that has undergone secondary changes. In none of the cases reported was a compression of the spinal cord observed.

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11. von Pechy, Koloman: Zur Kenntnis der gutartigen Wirbelsäulengeschwülste im Wirbelkanal, Frankfurt. Ztschr. f. Path. **37**:562, 1929.

The posterior cartilage nodes are extensions of some of the fibers of the nucleus pulposus into the spinal canal. Normally, the nucleus pulposus is situated at the junction of the middle and posterior third of the vertebral body and is separated from the spinal canal by the posterior fibers of the annulus fibrosus and the posterior longitudinal ligament. As a result of a severe trauma or degenerative changes of

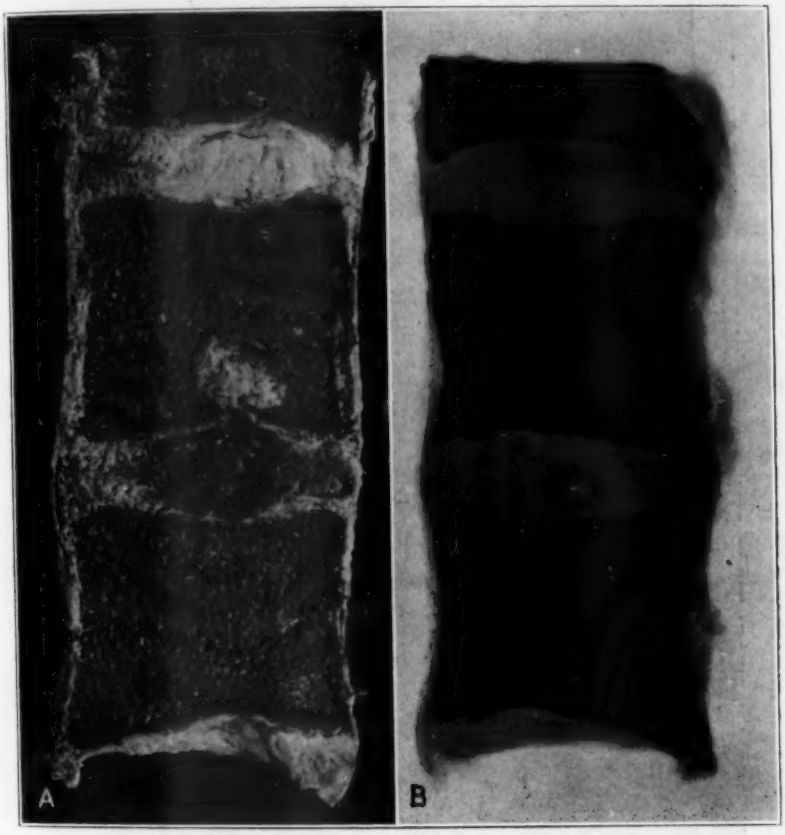

Fig. 6.—*A* shows partially degenerated and cystic disk node. *B*, a roentgenogram of section *A*, presents a faintly visible small area of osteoporosis.

the annulus fibrosus, an avenue may be established for the extension of the expansile fibers against the posterior longitudinal ligament. The extent of the invasion of the spinal canal is on the whole very slight, yet it is conceivable that the disk extensions may be of such size as either to compress the cord directly, or, by becoming loose in the spinal canal, to produce pressure symptoms. Dandy [12] reported two cases in which loose cartilage from the intervertebral disk produced a compression of

12. Dandy, Walter E.: Loose Cartilage from the Intervertebral Disk Simulating Tumor of the Spinal Cord, Arch. Surg. **19**:660 (Oct.) 1929.

the cord, which resulted in paralysis of both lower extremities. The patients were men, aged 47 and 61 years, respectively. The paralysis followed an injury to the back. A laminectomy was performed, and a piece of loose cartilage was found in the spinal canal. Following the operation, the paralysis disappeared.

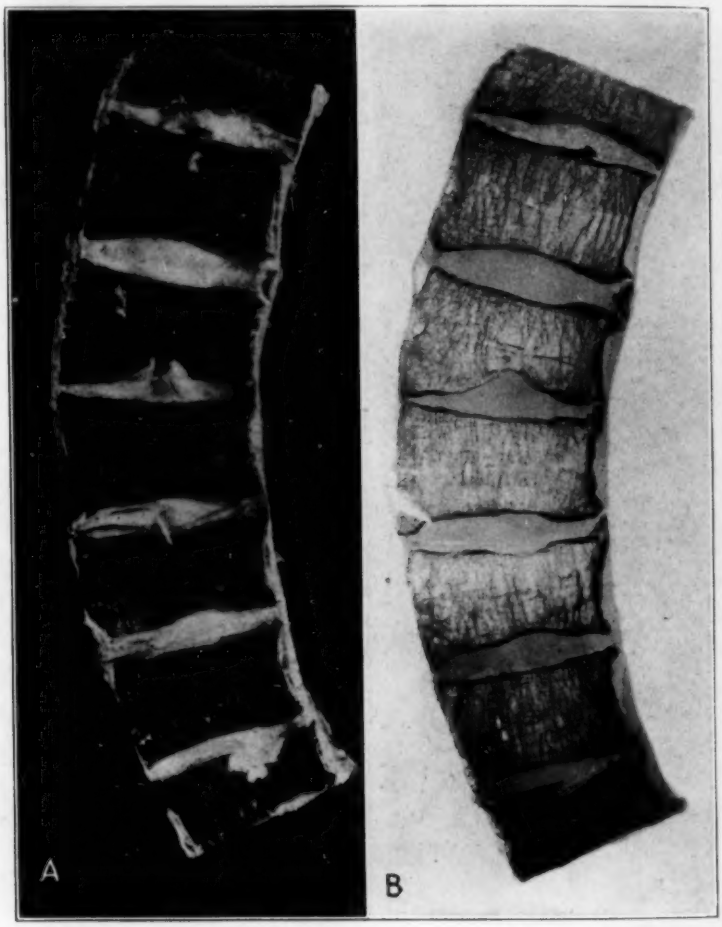

Fig. 7.—*A* shows disk extensions in the third and last segment. *B*, a roentgenogram of section *A*, shows two defects in the respective bodies.

ROENTGEN STUDIES OF INTERVERTEBRAL DISK NODES

Pathologic specimens consisting of fairly large cartilage nodes in the adjacent vertebral bodies with defects in the cortical plate or surrounded by a dense layer of compact bone are clearly seen on lateral roentgenograms. They appear as small areas of lessened density

surrounded by a dense shadow. A break in the continuity of the cortical plate is nearly always noted on the film. Posterior cartilage nodes when not calcified or ossified are not visualized. Chasin,[13] in experiments on the cadaver, demonstrated that structural changes in the vertebral bodies had to be of considerable size to be noted on the roentgenogram. He found that defects of from 1 to 1.5 cm. in diameter could not be seen.

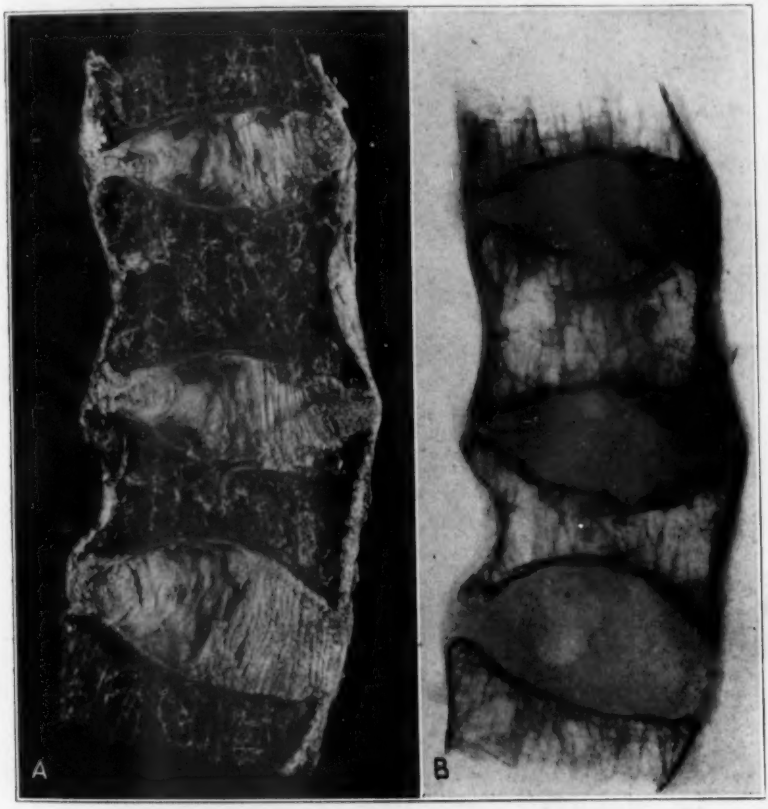

Fig. 8.—*A*, is a section through the lumbar bodies of a markedly osteoporotic spine. The intervertebral disks are ballooned out. *B* is a roentgenogram of section *A*. Note the extreme osteoporosis and compression or "hourglass" appearance of the bodies.

To determine the extent of roentgen visualization of the cartilage nodes, roentgenograms were made of a number of pathologic specimens with clearly outlined disk nodes. Figure 3*A* is a photograph of a

13. Chasin A.: Die Dimensionen der destruktiven Veränderungen in den Wirbelkörpern die röntgenographisch bestimmt werden können, Fortschr. a. d. Geb. d. Röntgenstrahlen **37**:529, 1928.

sagittal section of several vertebral bodies, and presents three rather large disk extensions in the bodies. The upper and middle disk nodes are white and glistening and have a soft elastic consistency, while the lower node is cartilaginous and in places ossified. In the roentgenogram (fig. 3 *B*), the upper disk extension presents a semicircular depression

Fig. 9. (case 1).—Lateral view showing a depression of the upper surface and a large vacuolated area within the lower half of the third lumbar body.

or area of erosion in the body. The middle disk node can barely be seen. The distal node presents a dense semicircular shadow with evidence of bone production. On the contiguous portion of the adjacent vertebra is a small irregular shadow which is fairly indicative of an ossified node.

Figure 4 *A* presents irregular calcified cartilage nodes. In the roentgenogram, the small irregular upper node is indistinct and can just barely be seen, while the lower node presents a dense irregular semicircular shadow. A comparison of figures 3 *B* and 4 *B* shows that in the former the changes in the bodies are largely destructive, whereas

Fig. 10 (case 2).—Note the large defect in the proximal cortical plate of the twelfth dorsal segment.

in the latter, the invading cartilage has been converted into a dense calcific structureless node. In section 5 *A*, one notes over the lower bodies two degenerated cartilage nodes surrounded by thick compact bone. In the roentgenogram (fig. 5 *B*), they appear as areas of lessened density limited by a dense sclerotic border. Figure 6 *A* presents

a large, isolated and more or less degenerated cartilage node in the vertebral body. In the roentgenogram (fig. 6 *B*), this area is only faintly visible as a zone of osteoporosis. In the specimen shown in figure 7 *A*, a disk extension in the third body and a larger disk node in the seventh body is clearly seen. In the roentgenogram (fig. 7 *B*), the

Fig. 11 (case 3).—Note the semicircular area of lessened density in the lower and posterior half of the eleventh and twelfth dorsal and first lumbar bodies. Note also the patchy appearance of the second lumbar body.

disk extensions are presented as fairly large defects in the third and seventh vertebral bodies of this specimen. Figure 8 *A* is a photograph of a sagittal section of a markedly osteoporotic spine. The intervertebral disks are ballooned out, and the vertebral bodies compressed. Between

the two lower intervertebral disks the body has been compressed and presents an "hourglass" or "fish vertebrae" appearance. In the roentgenogram (fig. 8*B*), the bodies appear atrophic and reduced in size, while the intervertebral disks have ballooned out. One should note also the apparent collapse of the bodies and the extreme osteoporosis.

Clinically, the cartilage nodes are seen in the lateral roentgenogram in only a very small number of cases. Dittrich,[5] in a review of all the roentgenograms taken at Professor Bayer's clinic in Heidelberg, found cartilage nodes in only one plate. This case was in a man, aged 43, who fell from a considerable height and sustained a compression fracture of the ninth dorsal vertebra. The plates showed small semicircular defects in the cortical layers of the eighth dorsal and in the distal surfaces of the eleventh and twelfth dorsal and the first lumbar vertebrae. Mau,[6] of the Surgical University Clinic at Kiel, Germany, reported that in a review of all the roentgenograms of the clinic, he found in only one plate the presence of a cartilage node. The plate was of the back of a man, aged 40, who thirteen years before was struck on his back by a falling tree. In the lateral roentgenogram, a cartilage node was seen over the upper margin of the eighth dorsal vertebra. Müller [7] reported five cases in men varying in age from 21 to 40, in whom one or more cartilage nodes were found in the lateral roentgenogram. At the Hospital for Joint Diseases, in an examination of over 2,000 spines of which roentgenograms had been made for various reasons during the past three years, 9 cases of intervertebral disk extensions were found in 1 or more vertebral bodies.

REPORT OF CASES

CASE 1.—M. R., a woman, aged 26, was admitted to the hospital on July 17, 1929, with the complaint of severe pain over the lower part of the back. On April 10, 1929, she fell down a flight of stairs and injured her back. She was carried home and remained in bed for two weeks. She then got up, but still had severe pain over the back, and experienced difficulty in getting about. Examination revealed a slight elevation or knuckle formation over the third lumbar vertebra. Flexion of the lumbar spine was entirely restricted. There was slight tenderness over the third and fourth lumbar spinous processes and over the coccyx.

Roentgen Observations.—The third lumbar vertebral body was compressed. There was a definite depression over its upper surface, with a large, more or less irregular, vacuolated area the limits of which were demonstrated as a dense, sclerotic border within the third lumbar body (fig. 9). This picture was one of a traumatic extension of the intervertebral disk substance into the vertebral spongiosa.

CASE 2.—S. C., a laborer, aged 46, was admitted to the hospital on July 26, 1927, with the complaint of pain over the spine. On April 16, 1926, he fell off a scaffold and injured his back. He was taken into a local hospital in an unconscious state, and remained there for ten days. Since then, he has had severe pain in his back. He is unable to work, carry weights or walk without support.

Motion of the spine was restricted in all directions. There was a slight tenderness over the spinous processes of the eleventh and twelfth dorsal and first lumbar vertebrae.

Roentgen Observations.—There was a triangulation of the twelfth dorsal vertebral body with a solution of continuity of the proximal cortical plate. There

Fig. 12 (case 6).—Lateral view showing the semicircular areas of lessened density with sclerosed borders in the upper and lower end of the third lumbar vertebra.

was also a pea-sized area of lessened density in the spongiosa which was surrounded by a dense eburnated border (fig. 10).

CASE 3.—D. S., a cutter, aged 37, was admitted to the hospital with the complaint of pain over the lower part of the back. The patient gave a history of having lifted a heavy roll of cloth, after which he felt a sharp pain in the back

and was unable to straighten up. He had to be assisted and was taken home. Examination revealed a stiff, rigid spine.

Roentgen Observations.—Over the distal articular surfaces of the eleventh and twelfth dorsal and the first lumbar vertebrae were irregular, small areas of lessened density or disk extensions in the spongiosa. These areas were clearly visible and were bordered by a dense surrounding margin (fig. 11). The second lumbar vertebrae had an irregular shape with a patchy osteitis.

Comment.—In the cases cited a direct causal relationship between trauma and disk extensions in the bodies is evident. In the first two cases, the injury produced a partial collapse or compression of the vertebrae. The disk extensions involved a considerable portion of the bodies and were clearly seen in the lateral roentgenograms. In the third case, a preexisting pathologic condition as a structural weakness of the lower dorsal and lumbar bodies appears to have been present, which prior to the injury gave no symptoms. Trauma seems obviously to have had a direct precipitating effect in the production of the spinal picture.

CASE 4.—G. J., a school girl, aged 15, was admitted to the hospital with a tentative diagnosis of a tumor of the spinal cord. The patient stated that two weeks prior to her admission, she fell and injured her back. She complained of pain over the left thigh and the knee. The pain was worse at night. Examination revealed no impairment of the motion of the spine and no tenderness. There was a slight atrophy of the left thigh. The attending neurologist felt that the slight atrophy and pain were secondary to a radicular involvement. All laboratory tests were negative.

Roentgen Observations.—There were small irregular saw tooth areas on the surfaces of the second lumbar body and a larger semicircular depression over the twelfth dorsal vertebra.

CASE 5.—J. M., a shoe operator, aged 37, came to the outpatient department with a complaint of pain over his back. He said that the pain came on after bathing. It was intermittent and was worse in rainy weather. Flexion of the spine was slightly limited.

Roentgen Observations.—A small irregular defect or area of bone destruction was seen in the lower cortical plate of the tenth dorsal vertebra.

CASE 6.—E. D., a waiter, aged 53, was admitted to the hospital with a compaint of generalized rheumatic pains of over two years' duration. The patient walked slowly and with his body bent forward. Mobility of the spine was restricted in every direction.

Roentgen Observations.—Over the proximal and distal surfaces of the third lumbar vertebra were irregular deep depressions in the body (fig. 12).

CASE 7.—A. B., a salesman, aged 51, was admitted to the hospital with the chief complaint of pain over the right hip and back. Forward bending of the spine was limited and gave rise to pain.

Roentgen Observations.—Over the distal surface of the eleventh and proximal surface of the twelfth dorsal vertebrae were several irregular saw tooth areas of lessened density in the vertebral segments.

CASE 8.—D. O., a woman, aged 31, was admitted to the hospital with the complaint of backache. She had had acute intermittent attacks of pain in the back for the previous two years. Examination of the back revealed slight restrictions of movement and slight rigidity of the lumbar muscles. No local tenderness of the spinous processes was present.

Fig. 13 (case 8).—Small irregular depression in the upper posterior margin of the twelfth dorsal body.

Roentgen Observations.—Over the posterior third of the proximal surface of the twelfth dorsal vertebra was a bean-sized irregular area of lessened density surrounded by a sclerotic border (fig. 13).

CASE 9.—F. H., a woman, aged 70, was admitted to the hospital with the chief complaint of pain over the lower part of the back. The condition came on gradually about two years before. The patient was confined to bed for fourteen weeks. At the time of admission, the pain was severe and shooting. Examination of the back revealed a marked restriction of all movements.

Roentgen Observations.—The lumbar vertebrae were markedly osteoporotic. The bodies were compressed and resembled the so-called fish vertebrae (fig. 14).

Comment.—The etiologic factors involved in cases 4 to 8 are not definite. In case 4, a history of trauma was obtained, but its relationship

Fig. 14 (case 9).—Note the marked osteoporosis and moderate compression of the lumbar bodies.

to the disk nodes seemed very doubtful. The mode of onset, duration and type of pain in cases 5, 6 and 7, suggest an arthritic involvement of the spine, while in case 8, the well defined, clearly outlined disk extension appears suggestive of a traumatic origin. Case 9 presents atrophic or osteoporotic vertebral bodies in which the intervertebral disks of the lumbar segments were still active, and produced a slight compression of the bodies.

CLINICAL SIGNIFICANCE

The relationship of intervertebral disk extensions into the vertebral bodies to clinical signs and symptoms is as yet not definitely established. Schanz [4] expressed the view that the disk nodes lower the carrying capacity of the spine and in effect produce an "insufficient" vertebral column, or, as he terms it, an insufficientia vertebrae traumatica. He maintains that the disk extensions are of traumatic origin, and that the clinical picture may be explained by the pathologic observations. On the other hand, Schmorl [9] said that he feels that the presence of one or more cartilage nodes does not give rise to symptoms. The contention that these nodes diminish the carrying capacity of the spine, he dismissed on the ground that the area involved is usually so small that no appreciable disturbance is likely to occur. Schmorl expressed the belief that the cartilage nodes in young adults lead to the early development of spondylitis deformans. Müller,[7] in a report of five cases, found symptoms in only those persons showing multiple cartilage nodes in the roentgenogram. He maintained that the disk extensions are not per se responsible for clinical symptoms, but that basically a weakness or "insufficienz" of the vertebral bodies exists.

A preexisting pathologic condition or structural weakness of the vertebral bodies appears to be the underlying basis of a number of disk extensions. The precipitating factor in these cases is usually trauma. The patient who prior to the injury was free from symptoms soon thereafter develops pain and becomes partially or even totally incapacitated. In the lateral roentgenogram, disk extensions may be noted in several bodies, as seen in case 3 (fig. 11).

Müller's contention that only multiple disk nodes in the vertebral bodies give rise to symptoms seems inadequate. From my observations, intervertebral disk extensions of traumatic origin, whether single or multiple, give rise to clinical signs and symptoms. In other cases, symptoms arise only when a considerable portion of one or more vertebral bodies are invaded. In case 4, although more than one disk node was found, the area involved was small, and as a result no symptoms of the back were present. On the other hand, the clinical picture in case 9 is due to the reduced capacity of the spine, produced largely by the expansion of the disk substance into the atrophic vertebral bodies.

The demonstration of intervertebral disk nodes in the roentgenograms are of vital significance in medicolegal cases. Their recognition and correct interpretation are imperative. The presence of one or more disk nodes in the lateral roentgenogram of a patient who sustained an injury to the back may often explain the clinical picture. In these cases a direct causal relationship between trauma and disk extensions should be assumed to exist, unless roentgenograms taken before the

injury present the same pathologic changes. In all cases of painful and incapacitated spines due to disk extensions, the treatment is firm immobilization in a plaster of paris bandage jacket or by an Albee spine fusion.

SUMMARY

Intervertebral disk extensions or cartilage nodes are pathologic conditions of the spine. They are expansions of the elastic intervertebral disk substance into the adjacent bodies or into the spinal canal.

In the nine cases reported, trauma and degenerative or arthritic changes of the cartilaginous plate were the most important etiologic factors.

Roentgenographically, the disk extensions are seen as small areas of lessened density or small defects in the cortical plate and spongiosa.

Traumatic disk extensions into the adjacent vertebral bodies give rise to clinical signs and symptoms. In other cases symptoms arise only when a considerable area of the bodies is involved.

Intervertebral disk extensions into the spinal cord occur and may produce compression of the spinal cord.

ATROPHY AND FIBROSIS ASSOCIATED WITH LYMPHOID TISSUE IN THE THYROID

STRUMA LYMPHOMATOSA (HASHIMOTO)*

ALLEN GRAHAM, M.D.
AND
E. P. McCULLAGH, M.D.
CLEVELAND

Hashimoto,[1] in 1912, reported four cases of "a characteristic kind of chronic inflammation" of the thyroid which he designated struma lymphomatosa. He was unable to discover other cases of a similar nature in the literature. We are not aware that any cases corresponding to those described by Hashimoto have been reported as such since the original publication.

Subsequent observers either have failed to recognize or report this particular type of lesion, or have arrived at a different interpretation. The latter assumption seems the more probable, since recent writers[2] have stated that struma lymphomatosa is the early stage of Riedel's struma, despite the fact that Hashimoto carefully considered and definitely rejected such a relationship.

Four cases corresponding in every essential detail with those reported by Hashimoto have come under observation at the Cleveland Clinic. These are presented with the hope of stimulating others to record similar cases in order that the condition may be recognized as an entity, or that it may be brought into a proper relationship with other lesions of the thyroid characterized by atrophy of the parenchyma, replacement fibrosis and lymphoid infiltration or with inflammatory processes, bacterial or otherwise.

On account of the longer interval elapsing between the first examination and the operation in our cases we are able to contribute to Hashimoto's original observations the additional fact that the condition tends to progress rather than to retrogress, at least for a period of one year.

Our case 4 is the first one, so far as we know, in which the condition was correctly diagnosed clinically.

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1. Hashimoto, H.: Zur Kenntnis der lymphomatösen Veränderung der Schilddrüse (Struma lymphomatosa), Arch. f. klin. Chir. **97**:219, 1912.

2. Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 962.

REPORT OF CASES

CASE 1.—*History.*—On Dec. 14, 1923, a white woman, aged 75, registered at the Clinic complaining of a goiter which she had first noticed eight weeks previously. The goiter had gradually increased in size, the right side more markedly than the left. According to her son, a physician, the swelling was not accompanied by pain, disturbance of pulse rate or nervousness, the only symptoms being vertigo and occipital headaches. The vertigo was dependent on the position in which the arms and head were placed. There was no loss of weight. The patient had always been active and had not had any serious illness. She had borne four children, all of whom were living. Although she had lived for years in a district in which goiter was endemic, she had never had goiter, and there was no history of goiter in any member of the family.

Examination.—Examination revealed an elderly, well nourished woman without subjective or objective evidence of hyperthyroidism. There was no evidence of focal infection. All of the teeth had been removed and replaced by an artificial denture. The tonsils were small. The heart and lungs were normal. The right lobe of the thyroid was enlarged and hard, and there was a "rounded nodule"

Fig. 1 (case 1).—Anterior, mesial and cut surfaces of the right lobe of the thyroid.

in the median line. The temperature was 96.8 F., the pulse rate 60, and the blood pressure 120 systolic and 80 diastolic. The urine contained a trace of albumin, an occasional leukocyte, a few mucous threads and many epithelial cells. The roentgenologist reported that examination of the chest revealed "widening of the upper mediastinum, considerable exudative infiltration over the entire right lung, particularly in the lower lobe; exudative infiltration over the entire left lung, most marked in the apex. The infiltration is not unlike tuberculosis but may be the result of circulatory disturbance." The basal metabolism, blood counts, and Wassermann reaction of the blood were not recorded.

The clinical diagnosis was inoperable carcinoma of the thyroid.

Treatment and Operation.—Roentgen therapy was given over the thyroid area on December 15 and 16. The patient was sent home with instructions to return in from six to eight weeks.

On April 24, 1924, the patient reported at the clinic and it was noted that she had reacted well to the roentgen therapy. Her voice had been husky for a few weeks, but she had not experienced dysphagia, dyspnea or loss of weight. According to the history, there was "an irregular, nodular, hard enlargement of the thyroid, especially on the right side. The gland was well fixed." The tem-

perature was 99.3 F., the pulse rate 76, and the blood pressure 114 systolic and 68 diastolic. The urine contained an occasional cast and a few leukocytes. The basal metabolism was not recorded. The general physical observations were essentially similar to those noted four months previously. Although the goiter was thought to be malignant, there was no evidence of regional or distant metastases.

On April 25, the right lobe of the thyroid was resected under nitrous oxide-oxygen analgesia and procaine hydrochloride infiltration. After a low collar incision, the muscles were separated in the median line without transverse division. The gland was enlarged bilaterally, and was hard and fixed about the trachea. The right lobe was freed and brought out from its position behind the trachea. It was brittle, and the hemostats broke through without holding. The left lobe was not disturbed. The wound was closed around a flexible rubber drain.

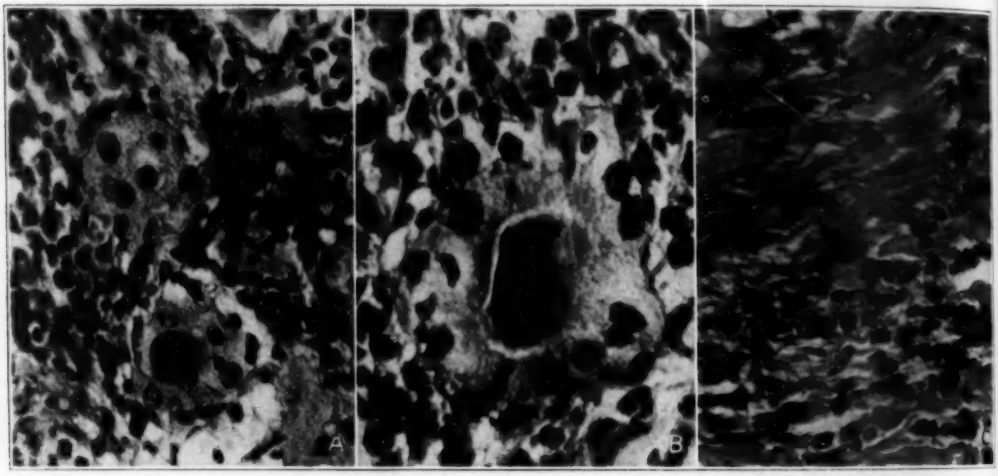

Fig. 2 (case 1).—*A*, atrophic thyroid vesicles and diffuse lymphoid infiltration; *B*, a phagocytic giant cell engulfing the colloid in a degenerating acinus; *C*, dense interlobular connective tissue and disappearance of the epithelium; reduced from a magnification of 600.

Pathologic Report.—The tissue consisted of the right lobe of the thyroid (fig. 1). It weighed 90 Gm. and measured 8 cm. vertically, 5 cm. transversely and 6 cm. anteroposteriorly. The lobe was considerably enlarged, uniform in structure and consistency and white, and had the contour of a normal lobe. Evidence of infiltration beyond the limits of the intact capsule was not seen. There was increased fibrous tissue resistance on cutting. The cut surface was finely and coarsely lobulated, and very cellular, with a diffuse increase of fibrous stroma. Neither normal thyroid tissue, colloid material, adenomas, nor areas of necrosis were recognizable grossly. Nothing to suggest a neoplasm was observed.

Microscopically, the tissue was divided into small and large irregular lobules separated by dense fibrous trabeculae of variable thickness (fig. 2 *c*). There was marked atrophy of the glandular tissue and replacement fibrosis to the point of complete disappearance of the epithelium in many lobules. In some areas, small,

pink-staining thyroid vesicles contained a small amount of colloid material (fig. 2 *A*). The nuclei of the epithelial cells varied considerably. Some were small and pyknotic; others were large and hyperchromatic. There was little to indicate active hyperplasia of the epithelium. Mitotic figures were not observed. An

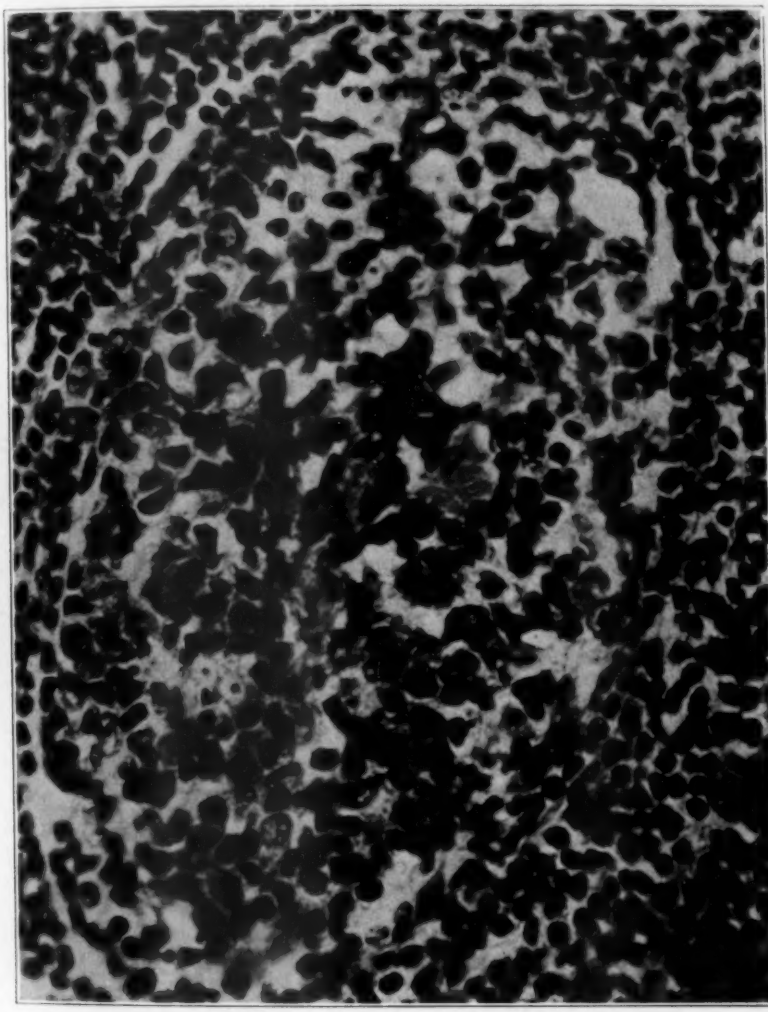

Fig. 3 (case 1).—Lymphoid tissue with hyperplastic germinal center; × 600.

extensive diffuse lymphocytic infiltration and numerous localized areas of lymphoid tissue with hyperplastic germinal centers (fig. 3) were present throughout; there were also a few scattered multinucleated giant cells of the foreign body type. Some of these were present in the acini (fig. 2 *B*), apparently phagocytosing the colloid material. There was no evidence of acute inflammation, abscess formation, tuberculosis, syphilis or neoplasm.

The pathologic diagnosis was exhaustion atrophy and fibrosis, with lymphoid infiltration of the thyroid.

Postoperative Course.—The immediate postoperative convalescence was uncomplicated. The temperature was slightly elevated, but returned to normal on the third day. The drain was removed on the day following operation, and the skin clips on the third day. The patient was discharged from the hospital on May 1, with the wound healed. Following operation she was given thyroxin, which was to be continued under the direction of her physician.

In September, the patient sustained a fracture of the arm as a result of a fall. She recovered satisfactorily.

On Feb. 12, 1926, a letter from the patient stated: "My condition now is very good, excepting my voice. That is husky, as if I had a cold. I think it took nearly a year to recover from my operation. Now I feel as well as I did ten years ago. I lost about 10 pounds but believe I have regained it. I began my business activities in a few weeks after my throat healed, but did not feel in a normal condition for a year."

On Dec. 12, 1929, a letter from the patient's son stated: "She is very well. I do not see any signs of hypothyroidism."

Comment.—One of us had an opportunity to examine the patient on the operating table immediately preceding anesthesia. It was noted that the face was swollen, the eyelids puffy and the skin thick and dry, with a definite pallor. The thyroid was enlarged bilaterally, without deformity of the lobes, and there was no evidence of extension to surrounding structures or involvement of cervical nodes. The thyroid did not impress the observer as malignant. After examination of the excised right lobe, it was suggested that the pathologic picture was consistent with clinical myxedema.

Unfortunately, information is not available concerning the amount of thyroxin or desiccated thyroid administered to the patient after her discharge from the hospital. The basal metabolic rate was not determined preoperatively or postoperatively.

Case 2.—*History.*—On Oct. 11, 1923, a white woman, aged 44, registered at the Clinic, with the history that eight months previously facial palsy had developed which she thought might be related in some way to a goiter that had been present for years. At the first observation she was recovering satisfactorily from the palsy. She complained of slight palpitation of the heart and dyspnea on exertion. She was not particularly nervous, had not lost weight and her appetite was good. There was no subjective or objective evidence of hyperthyroidism.

Examination.—The results of the general examination were negative, except for obesity, a sty on the left eye, probable dental infection and a "moderate-sized, inactive colloid goiter." The temperature was 98.6 F., the pulse rate 120, and the blood pressure 120 systolic and 70 diastolic. The heart, chest, abdomen and reflexes were normal. The blood counts, Wassermann reaction of the blood and basal metabolic rate were not recorded.

The clinical diagnosis was Bell's palsy (recovering), obesity and adenoma of the thyroid. Operation at a convenient time was advised.

On Oct. 20, 1924, the patient returned to the Clinic on account of pressure symptoms attributable to the goiter. The temperature was 98.2 F., the pulse rate 64, and the blood pressure 144 systolic and 66 diastolic. The urine contained a few leukocytes. The patient was admitted to the hospital for operation with a diagnosis of simple goiter.

Operation.—On October 22, the lateral lobes and isthmus were resected under nitrous oxide-oxygen analgesia and procaine hydrochloride infiltration. After a low collar incision, the muscles were separated in the median line without transverse division. The thyroid was enlarged bilaterally and symmetrically. There was a slight increase in vascularity. The gland was somewhat paler than normal, suggesting the exhaustion type of hyperplasia. After the resection, the wound was closed around a gauze drain.

Pathologic Report.—The tissue consisted of the greater portion of the lateral lobes and isthmus of the thyroid, and weighed 120 Gm. (fig. 4). The right lobe measured 8 by 4 by 4 cm., the left lobe 6 by 4 by 3 cm. and the isthmus 4 by 3.5 by 2 cm. The lobes were considerably enlarged, the right more so than the left. The tissue was white and firm. The capsule was slightly thickened, and

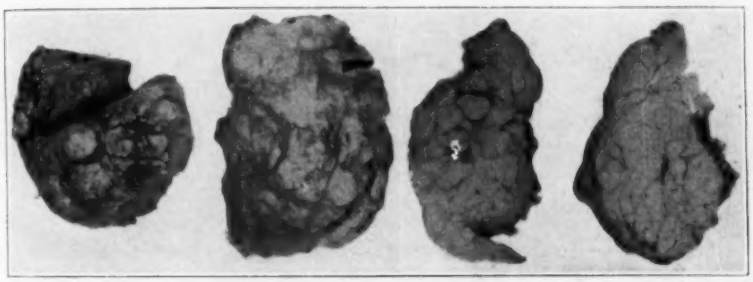

Fig. 4 (case 2).—External and cut surfaces of the right and left lobes. Note the fine and coarse lobulation.

the external surface was finely lobulated. On sectioning, increased fibrous tissue resistance was noted. The cut surface was white and finely and coarsely lobulated, with an increase of the fibrous stroma throughout. No normal thyroid tissue, colloid material or adenomatous tissue was recognizable grossly. There was nothing to suggest a neoplasm.

Microscopically, the tissue was divided into irregular areas by fibrous trabeculae of variable thickness traversing the gland from the capsule. The lobular arrangement of the thyroid was imperfectly maintained. In many of the lobules the epithelium was atrophic (fig. 5 *A*), and in a few it was entirely replaced by fibrous tissue (fig. 5 *B*). The remains of the acini were present as small clumps of fairly large, pale-staining, vacuolated cells and larger syncytia-like masses of cytoplasm containing several nuclei. Many of the epithelial masses contained small droplets of colloid and poorly preserved acini. There were extensive diffuse interlobular and intralobular lymphocytic infiltrations (fig. 5 *C*) and numerous large localized collections of lymphoid tissue with hyperplastic germinal centers. Mitotic figures or other evidence of active proliferation of the thyroid epithelium was not observed. Occasional multinucleated giant cells of the foreign body type were present in the areas in which the thyroid epithelium was undergoing atrophy.

There was no evidence of acute inflammation, abscess formation, tuberculosis, syphilis or neoplasm.

The pathologic diagnosis was atrophy and fibrosis of the thyroid, with extreme lymphoid infiltration. The pathologic picture suggested the possibility of clinical myxedema.

Postoperative Course.—The immediate postoperative convalescence was uncomplicated. The drain was removed on the day following operation; the skin clips were removed on the third day, and the patient was discharged from the hospital on the seventh day, with the wound discharging slightly.

On November 15, the basal metabolic rate was minus 43 per cent. The patient was given 2 grains (0.13 Gm.) of desiccated thyroid per day.

On Feb. 10, 1925, a letter from her physician stated: "The patient is feeling well, but complains of a swelling of the face and extremities." She was still taking desiccated thyroid for relief from the hypothyroidism.

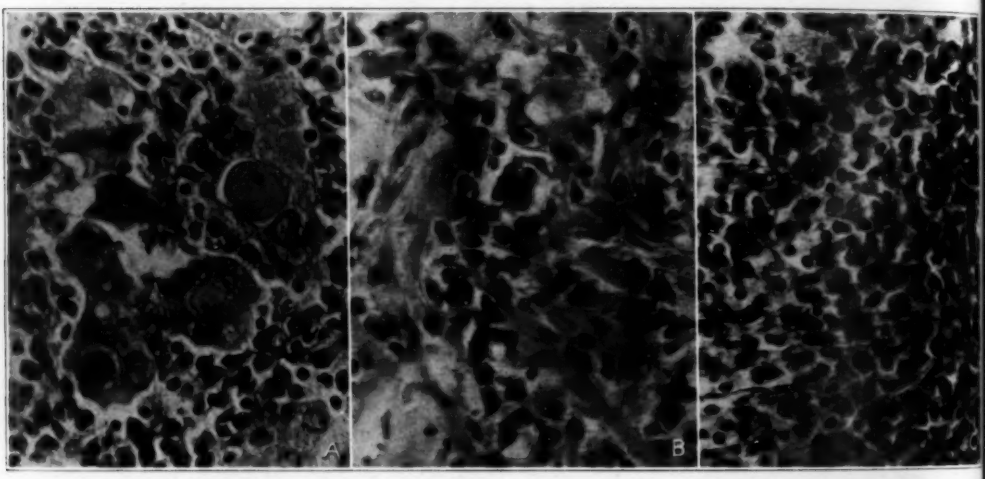

Fig. 5 (case 2).—*A*, degenerating acini and syncytia-like masses of epithelium; note the vacuoles and droplets of colloid; *B*, intralobular fibrosis with complete disappearance of the epithelium; *C*, diffuse lymphoid tissue; reduced from a magnification of 600.

On March 13, 1930, a letter from the patient stated that she had been troubled by hot flashes and sweating for eighteen months. Otherwise she was well when she took one tablet of desiccated thyroid per day.

Case 3.—*History.*—On Feb. 5, 1929, a white woman, aged 53, registered at the clinic complaining of a goiter which had been present for fourteen years. Four years previously the goiter had begun to increase in size, causing dyspnea and a sensation of choking. For one year the pressure symptoms had been increasing in severity, and the patient had been unable to lie on her back. The enlargement of the thyroid was not accompanied by pain, fever, cardiac symptoms, increased nervousness or increased excitability. The appetite had remained unchanged, and there was no loss of weight. The patient was married, had one child living and had had three miscarriages. The menopause had been passed six years previously.

Examination.—Physical observations were as follows: The patient was obese, weighing 195 pounds (90.5 Kg.). She had many crowned teeth and moderate pyorrhea. The tonsils were enlarged and the pharynx red, but there was no general lymphadenopathy. The skin was of normal texture. The history stated that "the thyroid was greatly enlarged, soft and nodular." The breath sounds over the lungs were wheezy and harsh. There were no râles, friction rubs or areas of increased density. The heart was slightly enlarged to the left. No murmurs were heard. The vocal cords were normal. The temperature was 98.6 F., the pulse rate 80, and the blood pressure 215 systolic and 150 diastolic.

The urine had a specific gravity of 1.036, and contained albumin and numerous leukocytes. The blood sugar amounted to 96 mg. and the blood urea to 30 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was negative. The red blood cells numbered 4,100,000 and the white blood cells 6,800; the

Fig. 6 (case 3).—Artist's sketch showing the high position of the upper poles and extension posterior to the trachea, with distortion and compression of the latter.

hemoglobin was 70 per cent, the neutrophils 65 per cent, the small lymphocytes 30 per cent and the large lymphocytes 5 per cent. The basal metabolic rate was not determined.

The clinical diagnosis was adenomatous goiter with tracheal compression, obesity and pyorrhea alveolaris. The patient was admitted to the hospital for operation.

Operation.—On February 12, the lateral lobes and isthmus were resected under nitrous oxide-oxygen analgesia and procaine hydrochloride infiltration. After a low collar incision, the muscles were separated in the median line without transverse division. The right lobe of the thyroid was from four to five times the normal size and extended behind the trachea. The left lobe was only slightly smaller than the right, and also extended behind the trachea (fig. 6). The wound was left open, and an acriflavine gauze pack was applied.

Pathologic Report.—The tissue consisted of the greater portion of the lateral lobes and isthmus of the thyroid; the weight was 175 Gm. (fig. 7). The left lobe measured 8.5 by 4 by 4 cm.; the right lobe, 9 by 3 by 4 cm.; the isthmus, 3 cm. transversely, 6 cm. vertically and 3 cm. anteroposteriorly. The gland as a whole was greatly enlarged, white and firm. The normal contour of the lobes

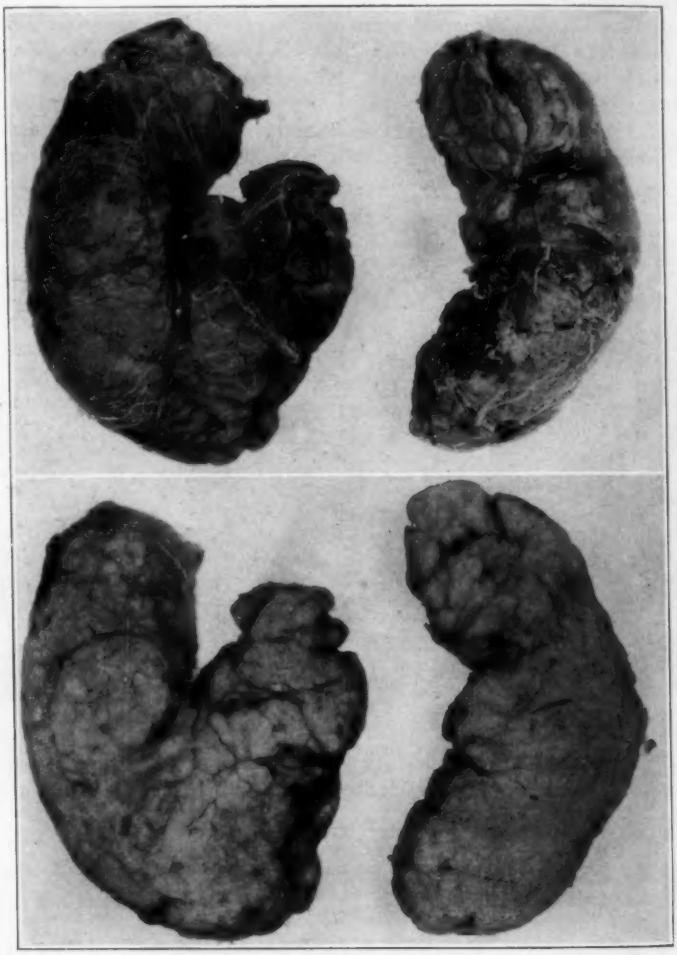

Fig. 7 (case 3).—External and cut surfaces of the right and left lobes. Note the well preserved contour of the lobes.

was maintained. Numerous fine blood vessels were present in the slightly thickened capsule. There was increased fibrous tissue resistance on sectioning. The cut surface was finely and coarsely lobulated. No normal thyroid tissue, colloid material, adenomas, cysts or areas of necrosis were recognized grossly. There was nothing to suggest a neoplasm.

Microscopically, the lobular structure of the thyroid was indefinitely maintained. The lobules were separated by thick trabeculae of dense fibrous tissue. A diffuse fibrosis of many of the lobules (fig. 8 *c*) and well marked atrophy and degenerative changes in the epithelium (fig. 8 *a*) were noted. There was an extensive interlobular and intralobular lymphocytic infiltration, also numerous large localized areas of lymphoid tissue with hyperplastic germinal centers. Many pseudotubercles, apparently resulting from fibrosis and phagocytosis of the degenerating epithelium and colloid material, were present, together with a moderate number of eosinophilic leukocytes, but no plasma cells. There were numerous large multinucleated foreign body giant cells, some of which contained droplets of colloid material (fig. 8 *b*) and epithelial débris. Mitotic figures or other indications of active proliferation of the epithelium were not observed. There was no evidence of a neoplasm.

The pathologic diagnosis was exhaustion atrophy and fibrosis with lymphoid infiltration of the thyroid.

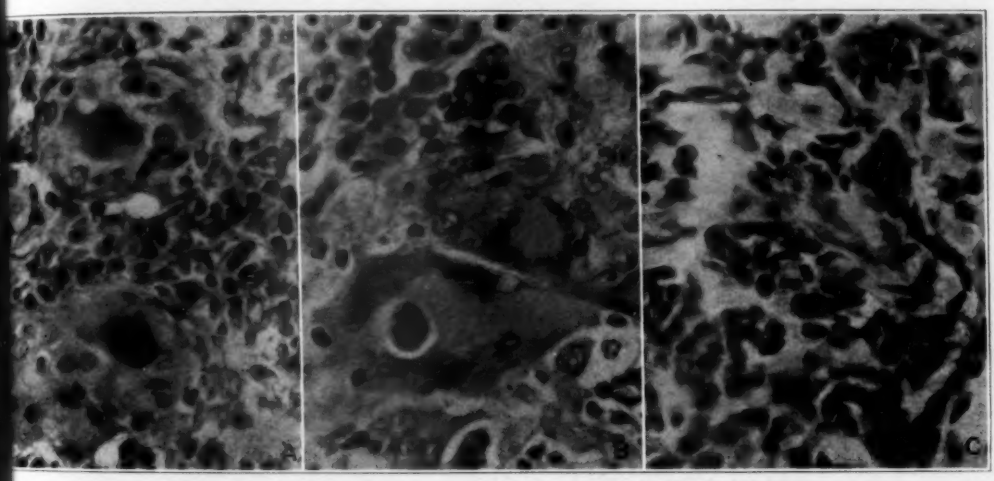

Fig. 8 (case 3).—*A*, degenerating epithelium and lymphoid infiltration; *B*, large multinucleated giant cell engulfing the colloid; phagocytosis of the epithelium at the bottom; *C*, young connective tissue replacing the atrophic epithelium; reduced from a magnification of 600.

Postoperative Course.—The immediate postoperative convalescence was complicated by infection of the wound, following secondary closure on the day after the operation. The basal metabolic rate was minus 9 per cent on the ninth postoperative day. There was a purulent exudate from the wound at the time of discharge from the hospital on the eleventh postoperative day. The patient has not been heard from since her discharge from the hospital.

Case 4.—*History.*—On July 11, 1929, a white woman, aged 72, was seen in consultation with reference to a goiter that had been considered malignant by other consultants. The following history was obtained:

Six months previously, following an attack of "influenza," she had noticed a painful enlargement of the thyroid associated with tenderness over the gland, with fever. At the onset the goiter had been soft, but gradually it had become hard and had remained so.

Examination.—There was moderate uniform bilateral enlargement without evidence of hyperthyroidism or interference with deglutition or respiration. Inspiratory stridor, however, was marked. The gland was hard throughout, closely attached to the trachea and not adherent to surrounding structures. The lobes had a normal contour and there were no nodules, thrill or bruit. Cervical and general lymphadenopathy were absent. The lower extremities were slightly edematous. The only roentgenographic observations in the chest were enlargement of the heart and fibrosis in the hilus of each lung. There was no evidence of metastasis.

The clinical diagnosis was thyroiditis (struma lymphomatosa). Operation was advised.

Second Examination.—On November 6, the patient returned to the clinic, having had no treatment since the previous examination. The additional data obtained were as follows: She was born in Ireland, came to the United States at the age of 15, and had lived in Cleveland ever since. She had never had goiter, and there was no history of goiter in her family. The patient was obese, weighing 189 pounds (85.6 Kg.). The temperature was 98.6 F., the pulse rate 84, and the blood pressure 135 systolic and 100 diastolic. Since the previous examination there had been further enlargement of the thyroid, particularly on the right side. The inspiratory stridor was more marked, and the voice had become husky. Laryngoscopic examination revealed evidence of pressure on the larynx anteriorly, obscuring the arytenoid folds. The vocal cords were normal. Roentgenograms of the chest showed enlargement of the heart and marked pneumocardiac fibrosis in the lungs. A blood count showed: red blood cells, 3,750,000; white blood cells, 5,200; hemoglobin, 70 per cent; neutrophils, 65 per cent; small lymphocytes, 30 per cent, and large lymphocytes, 5 per cent. The Wassermann and Kahn reactions of the blood were negative. The blood sugar content was 99 mg. and the blood urea, 24 mg. per hundred cubic centimeters. The basal metabolic rate was plus 18 per cent. The kidneys excreted 65 per cent of phenolsulphonphthalein in two hours. Roentgenograms of the teeth revealed pyorrhea and dental caries.

Operation.—The patient consented to operation and was admitted to the hospital, where repetition of the basal metabolic test and blood count revealed the following: basal metabolic rate, plus 21 per cent; red blood cells, 4,140,000; white blood cells, 9,100; hemoglobin, 70 per cent; neutrophils, 67 per cent; small lymphocytes, 30 per cent and large lymphocytes, 3 per cent.

On November 11, the left lobe of the thyroid was resected under nitrous oxide-oxygen analgesia and procaine hydrochloride infiltration. After a low collar incision, the muscles were separated in the median line without transverse division. The left lobe was exposed and found to be hard, and symmetrically enlarged about six times the normal size, with preservation of the normal contour. There were no adhesions between the lobe and the adjacent tissues. During resection of the left lobe it became necessary to divide the preglandular muscles transversely in order to deliver the upper pole. Since operation was undertaken for relief from obstruction and the lesion was found to be nonneoplastic, it was considered unnecessary to resect the enlarged right lobe. The wound was closed around a rubber-tissue drain. A transfusion of 500 cc. of whole blood was given shortly following operation.

Pathologic Report.—The tissue removed consisted of the left lobe of the thyroid; the weight was 105 Gm. (fig. 9). It measured 9 cm. vertically, 5 cm. transversely and 6 cm. anteroposteriorly. The lobe was greaty enlarged and the normal contour was maintained. The external surface was coarsely irregular, but not nodular. The capsule was thickened, and a small amount of muscle tissue

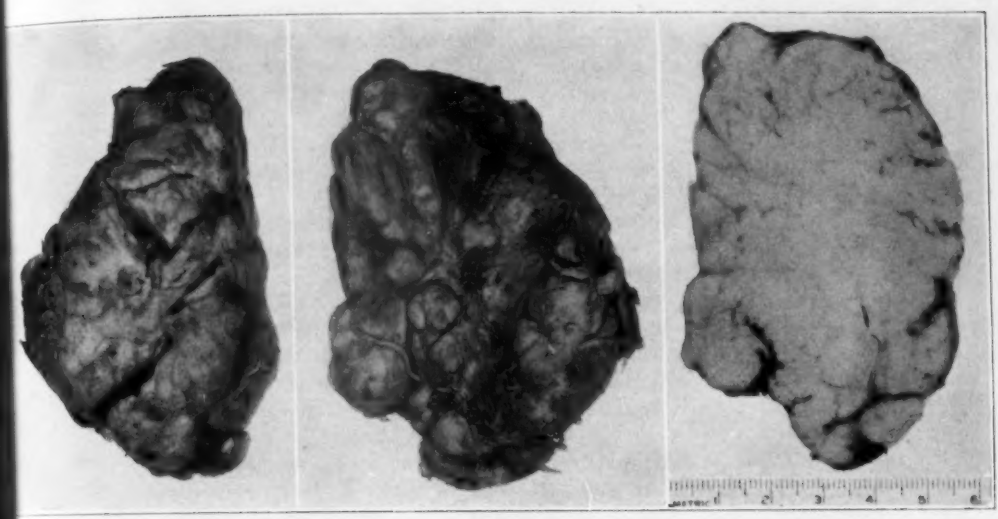

Fig. 9 (case 4).—Anterior, mesial and cut surfaces of the left lobe; lobulation obscured by the diffuse fibrosis.

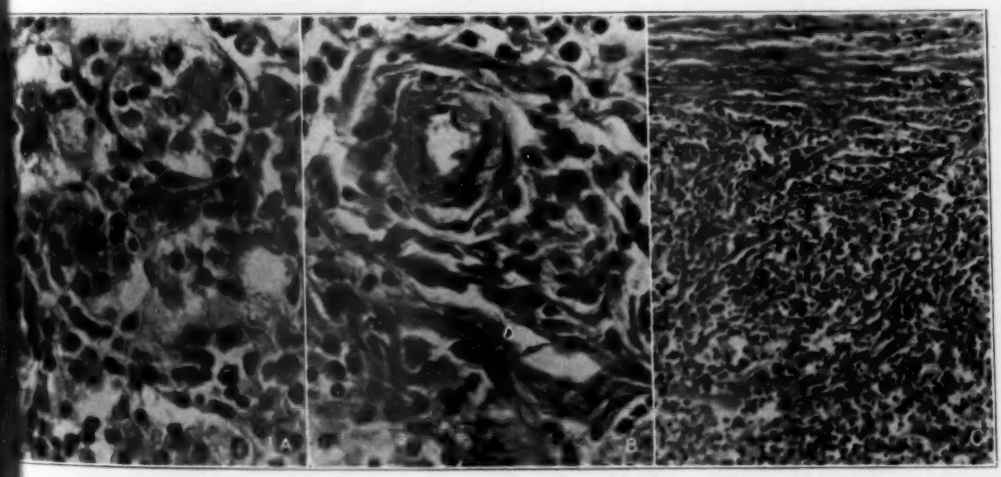

Fig. 10 (case 4).—*A*, degenerating acini and lymphocytic infiltration; *B*, epithelium being replaced by collagenous fibrous tissue; both *A* and *B* reduced from a magnification of 600; *C*, interlobular and intralobular fibrosis, with complete disappearance of the epithelium; reduced from a magnification of 200.

was loosely attached to the anterior surface. The tissue was uniform, firm, rubbery and white throughout. There was a deep groove on the mesial surface for the trachea. The vascularity was not great. On section, the gland cut with increased fibrous tissue resistance. The cut surface was finely and coarsely lobulated and very hard. No normal thyroid tissue, colloid material or adenomas were recognized.

Microscopically, sections from various portions of the lobe showed essentially similar changes. There was a marked diffuse increase of interlobular and intralobular fibrous tissue (fig. 10 *c*), with extensive atrophy of the thyroid epithelium. The lobular structure was indefinitely maintained, and in the lobules numerous pale-staining collections of thyroid cells were visible. In some areas these were arranged in small vesicles containing very little colloid (fig. 10 *a*). Throughout the gland there was a diffuse infiltration of lymphocytes (fig. 10 *a*) and a few localized collections of lymphoid tissue with relatively inactive germinal centers. No eosinophils, plasma cells or leukocytes were present. The tissue as a whole was poorly vascularized, but sclerosis of the blood vessels was not notable (fig. 10 *b*). There was no evidence of acute inflammation, syphilis, tuberculosis or neoplasm.

The pathologic diagnosis was chronic thyroiditis of the Hashimoto type.

Postoperative Course.—The immediate postoperative convalescence was uncomplicated. The drain was removed on the first postoperative day and the clips on the third day. There was a slight amount of serum in the wound. The vocal cords were normal following operation. The patient was discharged from the hospital on the sixth day with the wound healed, the temperature normal, the pulse rate from 80 to 90, the blood pressure 110 systolic and 70 diastolic, and the weight 150 pounds (68 Kg.).

On December 6, the basal metabolic rate was plus 20 per cent, the pulse rate 90 and the weight 180 pounds (73.6 Kg.). The urine contained a trace of albumin and an occasional leukocyte.

On Jan. 30, 1930, the basal metabolic rate was plus 11 per cent, the pulse rate 88, the weight 188 pounds (85.2 Kg.) and the temperature 97.2 F.

SUMMARY OF EIGHT CASES

The table is a brief compilation of clinical data from the four cases reported by Hashimoto and the four observed by us.

All of the cases occurred in women. At the time of first examination the youngest was 40 years of age, the oldest was 76, and the average age was approximately 55.

None of Hashimoto's patients had lived in a goitrigenous district. All of our patients had lived for years in a district in which goiter is endemic. A history of goiter in the family was not obtained in any case.

In cases 1 to 5 in the table the discovery of the goiter marked the beginning of the complaint, and the duration of the goiter at the first examination varied from three days to seven months, with an average of approximately two and a half months. In cases 6, 7 and 8, asymptomatic goiter of eight months' to many years' duration antedated the complaint. In two of these cases 6 and 7, the onset of symptoms was not accompanied by any appreciable change in the goiter. In the third,

case 8, following influenza [3] the onset of symptoms was associated with an increase in the size of the goiter, pain, tenderness and fever. Possibly the longer duration of the goiter and symptoms in our cases as compared with those of Hashimoto may be related in some way to residence in a goitrigenous district.

Struma Lymphomatosa (Hashimoto): A Compilation of Clinical Data from Eight Cases

Case, Date Examined, Author	Sex Age	Duration Symptoms	Clinical Diagnosis	Operation	Postoperative Course
1 11/21/07 Hashimoto	F61	Goiter 7 months; no symptoms	Struma parenchymatosa	11/22/07 Bilateral resection	Fatigue and hoarseness following operation; 3/7/11, well
2 5/30/09 Hashimoto	F40	Goiter 40 days; symptoms 30 days; dysphonia, headache, disturbed appetite	Struma maligna (?)	7/2/09 Bilateral resection	Weakness and inability to work for 9 months; 1/27/11, face anemic, moderately nourished; ankylostomiasis
3 6/10/05 Hashimoto	F55	Goiter and symptoms 1 month; headache and sense of constriction about shoulders	Struma fibrosa	6/20/05 Bilateral resection	Hoarseness, weakness, anorexia, coldness, recurring edema improved by thyroid therapy; 3/20/11, slight hoarseness; no recurrence of goiter
4 9/19/07 Hashimoto	F45	Goiter 3 days; no symptoms	Struma fibrosa	10/20/07 Bilateral resection	Persistent weakness and edema of face; recurrence and regression of goiter; 3/10/11, voice husky; thyroid swollen and firm
5 12/14/23 Graham and McCullagh	F75	Goiter and symptoms 8 weeks; headache, vertigo; hoarseness after roentgen treatment	Carcinoma, inoperable; roentgen treatment; operation 4 months later	4/25/24 Resection right lobe, Wt. 90 Gm.	Voice husky; hypothyroidism; relieved by thyroxin; recovery in one year; 12/12/29, well
6 10/11/23 Graham and McCullagh	F45	Goiter many years; symptoms of pressure, palpitation, dyspnea	Adenomatous goiter	10/22/24 Bilateral resection, Wt. 120 Gm.	Hypothyroidism; basal metabolic rate −43%; improved by desiccated thyroid; 3/13/30, symptom-free on one tablet daily
7 2/5/29 Graham and McCullagh	F53	Goiter 14 years; increasing 4 years; dyspnea and choking sensation	Adenomatous goiter, without hyperthyroidism	2/12/29 Bilateral resection, Wt. 175 Gm.	Trace lost
8 7/11/29 Graham and McCullagh	F72	Goiter 14 months; symptoms 6 months (following influenza); pain, tenderness, fever, stridor and husky voice	Struma lymphomatosa	11/11/29 Resection left lobe, Wt. 105 Gm.	Recent case, gradually improving; basal metabolic rate: 12/6/29, +20%; 1/30/30, +11%

The symptoms associated with the goiter have been variable, inconstant and, with few exceptions, not pronounced. In two cases, 1 and 4, there were no symptoms other than the goiter. In the remaining six cases the following symptoms were recorded: headache in 3 cases, vertigo in 1, palpitation in 1, disturbance of appetite in 1, pain, tender-

3. This is the only case in the series in which a definite history and physical signs of an acute infection were associated with the onset of the symptoms.

ness and fever in 1, a sense of constriction in the shoulders in 1, hoarseness in 1 (following roentgentherapy), dysphonia in 2, inspiratory stridor in 1, dyspnea in 2 and a choking sensation in 1. The symptoms noted might be ascribed almost entirely to compression (fig. 8) by the enlarged, hard thyroid. It is apparent that there were no symptoms sufficiently distinctive to be of diagnostic importance.

Well defined symptoms of hyperthyroidism have been absent in all cases. Painstaking inquiry into the past history in two of our cases failed to reveal any indication of antecedent hyperthyroidism.

Hypothyroidism was not recognized at the first examination or during the interval (up to one year) between examination and operation in any of the cases. In two of our cases (5 and 6) marked hypothyroidism followed operation. In neither of these do we know whether or not the hypothyroidism was present before operation. There are reasons for believing that it was present in case 5, in which roentgen therapy was instituted four months prior to operation. In Hashimoto's case 3, symptoms and signs suggestive of hypothyroidism were noted following operation. These symptoms decreased on administration of a preparation of thyroid gland. In other cases in the series, symptoms suggestive of hypothyroidism were noted, but the records are not complete enough either to establish or to exclude the condition.

All of the cases in our series occurred in women who were overnourished or obese. One of Hashimoto's patients was described as corpulent; two were moderately well nourished, and one was of large stature. There was no indication that weight was particularly increased with the onset of the goiter or the symptoms. Notable loss of weight and emaciation were not observed.

Chronic or focal infections were noted as follows: leukorrhea for twenty years in Hashimoto's case 2; questionable dental infection in our case 2; pyorrhea alveolaris, enlarged tonsils and a red pharynx in our case 3, and pyorrhea and dental caries in our case 4.

Tuberculosis and syphilis were excluded clinically in all of Hashimoto's cases. In one of these the tuberculin and Wassermann reactions were negative eighteen months after operation. There was no clinical evidence of syphilis in any of our cases. The Wassermann reaction was negative in two of these and not recorded in two. In two of our cases roentgenographic examination of the chest suggested the possibility of pulmonary tuberculosis, but in each case an alternative interpretation was equally warranted.

Disturbances of the cardiovascular apparatus, in the sense of overactivity or incompetence, have not been prominently associated with the clinical course of the disease prior to operation. Such phenomena as general weakness, dyspnea on exertion, edema of the lower extremities,

arteriosclerosis and the presence of a trace of albumin, occasional casts and a few leukocytes in the urine were not more frequently encountered or of greater intensity than might be expected in an equal number of patients of similar age. In three of our cases the blood pressure did not exceed normal limits. In one case (our case 3), at the first examination the pressure was recorded as 215 systolic and 150 diastolic, and a tentative diagnosis of hypertonus was made. On the patient's admission to the hospital the same day, the pressure was 170 systolic and 106 diastolic. Two days later it was 164 systolic and 100 diastolic. Preceding operation five days later, it was 130 systolic and 70 diastolic. It remained normal after operation.

The accompanying table indicates the clinical diagnoses made and the operations performed in the eight cases. One of Hashimoto's cases was thought to be malignant, and in all of our cases the question of malignancy was raised either preoperatively, at operation or by the pathologist. One of our patients was thought to have an inoperable carcinoma. In our fourth case the goiter had been considered by other consultants to be malignant. The consistency of the goiter more than any other feature suggested the possibility of a malignant neoplasm. At the same time, the absence of definite indications of malignancy, such as extension beyond the capsule, involvement of cervical lymph nodes and evidence of distant metastases, indicated clearly the necessity of considering in the differential diagnosis some type of chronic thyroiditis or Riedel's struma.

At operation in each of our cases, the surgeon was confronted with the problem of determining whether the lesion was a diffuse carcinoma, a lymphosarcoma, a Riedel's struma or a nonspecific type of thyroiditis. In none of these is it usual to find a uniform bilateral enlargement of the thyroid without deformity of the lobes and without adhesions to surrounding structures. These physical features distinguish struma lymphomatosa from all of the aforementioned lesions.

Technical difficulties with the operative procedures have not been pronounced, principally because of the lack of adhesions to overlying structures. The glands have been closely attached to the trachea, and in some instances have extended high in the neck and posterior to the trachea (fig. 7). For these reasons, dislodgement of the lobes is difficult, but may be facilitated by transverse division of the muscles (our case 4). Hemorrhage during operation has not been alarming. Bilateral resection is probably the procedure of choice, although a resection of one lobe relieved the condition in our first case, and was performed in our last case too recently to evaluate the result.

Except for hypothyroidism (vide supra), the occurrence of which we would emphasize particularly, postoperative complications and

sequelae have not been serious. Our experience is in accord with Hashimoto's observation that huskiness of voice is persistent and distressing. In none of the cases has paralysis of the vocal cords been noted.

Restoration to health has been slow in all cases. Recovery required about one year in Hashimoto's cases. Our experience is in accord with this observation. We cannot urge too strongly that hypothyroidism be taken into consideration in all cases following operation. It seems probable that the administration of thyroxin or desiccated thyroid should hasten recovery, as it has been distinctly beneficial in two of our cases and in one of Hashimoto's.

Opportunities for observing the natural course of the disease have been limited. Not more than one month elapsed between the first examination and the operation in any of Hashimoto's cases. In none of these were noteworthy changes in the goiter or in the symptoms recorded during this interval. In two of our cases (1 and 4) the operation was performed four months after the examination. In each of these the symptoms increased in severity, and in one the goiter increased in size. In a third case (case 2) the operation was performed one year after the examination, and during this interval the symptoms became more pronounced, although any notable change in the goiter was not recorded. It appears, therefore, that the condition tends to progress rather than to retrogress, at least for a period of one year.

The pathologic observations in the eight cases were singularly in accord. The photographs and photomicrographs represent the process as observed in our cases (figs. 1 to 10).

Macroscopically there was uniform bilateral enlargement of the lateral lobes and isthmus of the thyroid. The gland as a whole was usually several times larger than normal (see table for weights) and was closely attached to the trachea. The capsule was intact, and was not adherent to overlying structures. In all parts a relatively normal contour was maintained. The gland was white and firm or hard; on cutting into it, the resistance seemed comparable to that of cirrhotic liver or fibromyoma of the uterus. The external surface was finely and coarsely irregular and without definite nodules. The cut surface was divided into irregular areas of firm white tissue by fibrous trabeculae of variable thickness passing into the gland from the capsule. The structure was uniform throughout the entire organ. In none of our cases were we able to recognize normal thyroid tissue or colloid material grossly. There were no nodules, tumor masses, adenomas, cysts, areas of calcification, abscesses or noteworthy areas of necrosis. The vascularization of the tissue was not great. The blood vessels were not prominent or particularly sclerotic.

Microscopically, the four patients examined by the authors had in common: well marked atrophy and degenerative changes in the epithelium, marked diminution in the colloid material, replacement fibrosis, extensive diffuse lymphoid infiltration and localized areas of lymphoid tissue with hyperplastic germinal centers, fibrous thickening of the capsule and marked increase of the interlobular and intralobular connective tissue. In none of our cases was there evidence of acute inflammation, abscess formation, tubercles, caseation or gummas. There was nothing to suggest a neoplasm of any kind. These observations, we believe, are in accord with those of Hashimoto. Further details as to the histologic variations in the individual cases are to be found in the case reports.

Macroscopically and microscopically, the process was such as to suggest that the thyroid was affected universally rather than in localized areas.

COMMENT

The nature of the process under discussion is obscure. No single clinical or pathologic feature of the condition is characteristic or pathognomonic. It is only when the record of the individual cases and of the series of cases as a whole is considered that the composite picture becomes sufficiently impressive to suggest that one may be dealing with an entity that hitherto has not received the attention it deserves.

A critical review of the case reports suggests that such clinical phenomena as have been observed are late manifestations of a well advanced pathologic alteration in the thyroid. The anatomic condition of the gland cannot be reconciled otherwise with the short clinical history. Neither the incipient stage nor the natural end-result has been recognized with certainty, and the condition has not been observed at autopsy, so far as we know.

An acceptable explanation of the pathogenesis of the changes in the thyroid is not apparent. It would be simple enough to follow the line of least resistance and agree with one of the prevailing views, namely, that struma lymphomatosa is the early stage of Riedel's struma. A review of the literature and personal experience with both types of lesions have inclined us to the view that they are quite dissimilar.

Riedel's struma more nearly approaches a true inflammation than does the lesion described by Hashimoto. In the majority of cases, Riedel's struma occurs in persons under 40 years of age; almost invariably the thyroid becomes adherent to surrounding structures, and the cervical tissues are usually extensively involved, even to the point of complete encasement of the carotid sheath and its contents; practically always it is a deforming lesion, and the outlines of the thyroid lobes are lost; it is frequently a unilateral or localized process; it is generally

surgically irremovable; it is usually associated with marked pressure symptoms; in many cases there are objective indications of long-standing goiter, notably in the form of adenomatous nodules and adenomas. In all of the foregoing respects Riedel's struma is in striking contrast to struma lymphomatosa. In view of such clearly defined differences, it is difficult for us to understand why it should be necessary to consider struma lymphomatosa as the early stage of Riedel's struma. It seems improbable that the early stage of a lesion should occur late in life and the late stage early in life.

From all standpoints, the nature and extent of the changes in the thyroid in struma lymphomatosa are far more suggestive of an end-result the cause of which is to be sought in a constitutional disturbance. Except for the degree and character of the constantly accompanying lymphocytic infiltration and lymphoid tissue, the process impresses us as a sclerosis, possibly comparable to cirrhosis of the liver or to nephrosclerosis. The fibrosis may be looked on as the natural result of atrophy and degeneration of the glandular tissue. The cause or causes of the primary parenchymal changes constitute a problem for future determination. The usual explanations for sclerosing processes are: exhaustion from overwork without an adequate period for recovery, interference with nutrition as a result of circulatory or trophic disturbances, and intoxications. All of these have as a primary effect degenerative changes in the cells or tissue, and fibrosis follows.

The lymphocytic infiltration and hyperplastic lymphoid tissue associated with the Hashimoto type of lesion is worthy of particular attention. That it is not specific is indicated by the fact that there appears to be no essential morphologic difference between the lymphoid tissue associated with struma lymphomatosa and that occurring in such diverse states as status lymphaticus, hypothyroidism, endemic goiter and hyperthyroidism. Of these four constitutional disorders, the lymphoid tissue in the thyroid in cases of hyperthyroidism more nearly resembles that observed in struma lymphomatosa.

We are aware that hyperthyroidism has not been recognized in any of the cases reviewed in this paper. Were it permissible to assume an antecedent hyperthyroidism, however, an explanation of the pathogenesis of struma lymphomatosa would not be difficult.

It is recognized that an insidious transition from hyperthyroidism to hypothyroidism and myxedema may occur. With the change, the thyroid undergoes exhaustion, atrophy and fibrosis. This corresponds to the so-called burned-out exophthalmic goiter. There are trustworthy indications that many cases pursue such a course and come under observation with the symptoms of myxedema well marked, but with the antecedent hyperthyroidism unrecognized. Year after year we are increasingly impressed with this fact.

In view of the foregoing considerations, it may be premature to exclude hyperthyroidism as a possible precursor of struma lymphomatosa. It is obvious that further experience is necessary before definite conclusions as to the etiology and pathogenesis can be drawn.

Pending the accumulation of further data, it seems not unreasonable to expect that the clinical recognition of struma lymphomatosa (Hashimoto) will increase if the striking peculiarities of the lesion are borne in mind. These may be summarized briefly as follows: (1) uniform bilateral firm or hard enlargement of the thyroid without notable deformity of the lobes and without definite nodules, (2) close attachment to the trachea without adherence to overlying structures, (3) occurrence in women in middle life or later, (4) absence of symptoms other than those that may be ascribed to moderate compression of the trachea, (5) absence of involvement of regional lymph nodes or evidence of distant metastases, (6) absence of impairment of the general health and (7) absence of signs of local inflammation.

CARCINOID TUMORS OF THE SMALL INTESTINE *

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There are two anatomic varieties of carcinoma of the small intestine: adenocarcinoma and carcinoid tumor. The former is more common than the latter, but both types are rare. The histogenesis of carcinoid tumors is obscure, and their clinical course is not generally understood. Many investigators have considered them benign, yet a number of cases in which metastasis occurred have been reported.

The purpose of this study is to report 11 cases of carcinoid tumors of the small intestine that have not heretofore been reported and to summarize the literature on the subject. Since metastasis was present in 3 cases, the series is divided into a malignant and a benign group.

MALIGNANT LESIONS [1]

CASE 1.—*History.*—A man, aged 67, had been operated on for cholelithiasis three years previous to admission. During the last year he had had persistent diarrhea with frequent, thin, watery stools. A dull, aching epigastric pain and a feeling of fulness had been present for an indefinite period. The appetite had been poor for the two weeks before death.

Necropsy showed strong fibrous adhesions connecting the liver, gallbladder, transverse colon and anterior wall of the abdomen. The appendix was retrocecal and normal. The mesenteric lymph nodes at the root of the mesentery were enlarged and fused into a large, irregular mass. The liver was greatly enlarged, weighing more than 2,500 Gm. The surface was somewhat nodular. Grayish masses, about 8 cm. in diameter, projected several millimeters from the surface. These nodules were scattered throughout the liver, but were especially numerous in the right lobe. Many small nodules, from 2 mm. to 1 cm. in diameter, could be seen just under the capsule of the liver. The nodules had slightly serrated margins, which were sharply defined. The centers of some of them were slightly depressed. On section, large grayish-yellow circumscribed masses were seen, which replaced a large part of the parenchyma of the liver. Some of the larger masses showed cystlike areas from 1 mm. to 1 cm. in diameter. These were filled with a translucent, gelatinous material.

In the upper part of the ileum was an ulcerated mass about 2 cm. in diameter. The margins were raised several millimeters above the surface of the mucosa.

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1. Cases 1, 2 and 4 are from the Department of Pathology, University of Minnesota, cases 3 and 5 to 11 are from the Mayo Clinic.

The center was ulcerated to a depth of 3 mm. The serosa opposite the lesion was thickened, glistening white and contracted. At one end of the mass at the root of the mesentery was a large calcareous nodule. The other portion was composed of grayish-yellow, firm tissue similar to that found in the liver.

Microscopic examination showed a compact mass of tissue replacing all the layers of the wall of the intestine. There was a large amount of fibrous tissue throughout the tumor. The inner zone was composed of numerous acini-like spaces and a few solid masses of cells. The acini-like spaces were large and were composed of two or more layers of cells. The lumina were round, oval, fusiform, or completely irregular. Goblet cells, Paneth's cells, acidophil cells or chromaffin cells could not be distinguished. The cells which formed the acini-like spaces and masses were peculiar, atypical, epithelial cells which had a superficial resemblance to the cells of Lieberkühn's crypts. In shape they were low cuboidal, quadrilateral

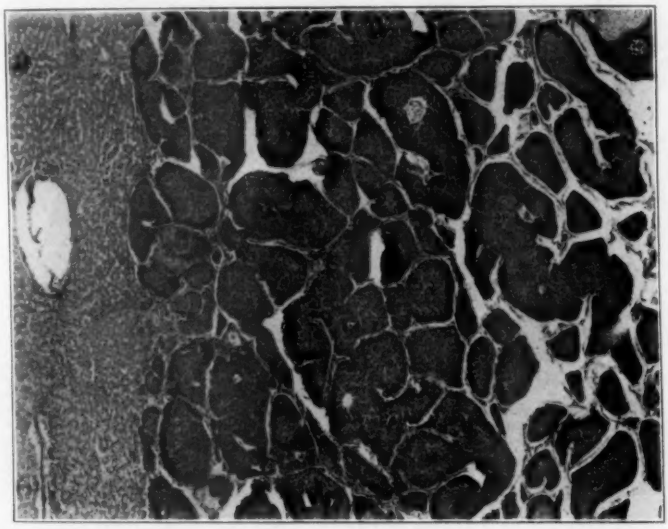

Fig. 1 (case 1).—Metastatic tumor in the liver from carcinoid tumor of the ileum (× 40).

or polyhedral. The cells varied only slightly in size. The basophilic cytoplasm was usually scanty, homogeneous and clear. The large nucleus was round to slightly oval. The nuclear membrane was prominent and coarse. The nucleus was vesicular and contained a moderate amount of punctiform chromatin. The solid masses of cells were composed of densely packed, small, similar polygonal cells. Mitotic figures were rare. There was considerable infiltration of lymphocytes and plasma cells. The moderately loose reticular stroma was composed of collagenous fibers. The middle zone of the tumor contained only a few small acini-like spaces. The cells were arranged in irregular blocks and masses. In some masses the peripheral cells were of a cuboidal or low cylindric shape, but most of them were polygonal. The cells were frequently so crowded that the nuclei were in contact. The stroma consisted of thick bundles of coarse collagenous fibers that enclosed the groups of cells in a netlike meshwork. Only a few small muscle fibers were present. There was no leukocytic infiltration. In the outer zone near the serosa, the solid groups of cells were flattened into columns, that

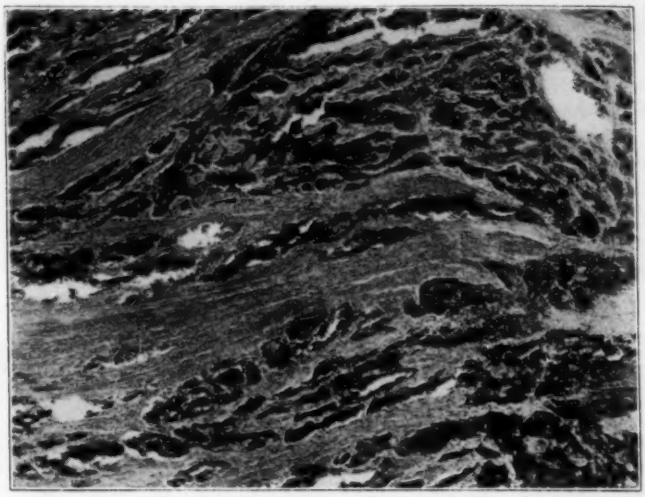

Fig. 2 (case 1).—Primary lesion of malignant carcinoid tumor of the small intestine; arrangement of cells in columns (× 40).

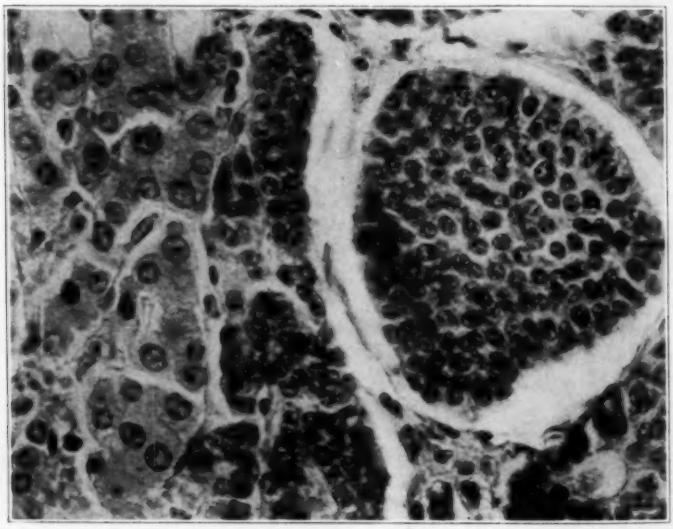

Fig. 3 (case 1).—Metastatic tumor in the liver from carcinoid tumor of the ileum (× 450).

is, thin strands or irregular cords of cells. The columns seemed arranged in a somewhat parallel fashion. Toward the serosa, the masses of cells tapered into a blunt point; there were occasional small alveolar masses. The cells were similar in appearance to those in the middle zone.

The metastatic nodules in the liver were rounded, sharply circumscribed masses of cells which compressed the adjacent parenchyma of the liver into atrophic bands. Each nodule consisted of numerous large, irregular sheets of cells. In or near the center of the largest sheets, there was either a capillary or a rounded space filled with a homogeneous smooth acidophilic mucinous substance. In other masses of cells there were irregular areas of central degeneration of variable size and shape. Capillaries were often seen in various parts of the masses. The

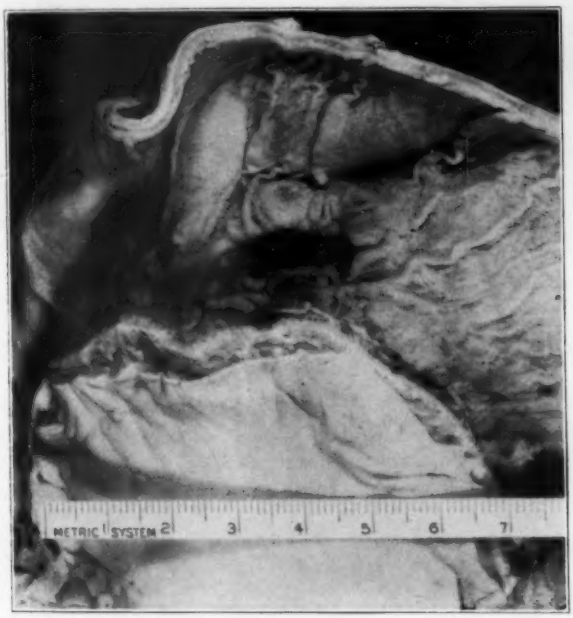

Fig. 4 (case 2).—A second primary nodule at the site of the anastomosis.

individual cells were polygonal and appeared identical to those in the primary lesion. The sparse stroma formed a loose incomplete network about the masses of cells, but did not encapsulate them. A few vessels ran in the connective tissue between the masses (figs. 1, 2 and 3).

Case 2.—*History.*—A woman, aged 65, was admitted to the hospital complaining of lack of appetite, belching of gas, nausea, vomiting, epigastric pain, flatulence, constipation and general weakness. Eight weeks before admission, the patient had been awakened during the night by intense pain in the middle of the epigastric region. The pain was sharp, intermittent and cramplike. The patient was nauseated, but did not vomit. Some relief was obtained by drawing up the knees on the abdomen. The attack disappeared in four hours. Three weeks after the first attack she had a second attack of severe pain, but at this time she vomited a yellowish fluid. After a short time the severe pain changed into a constant dull

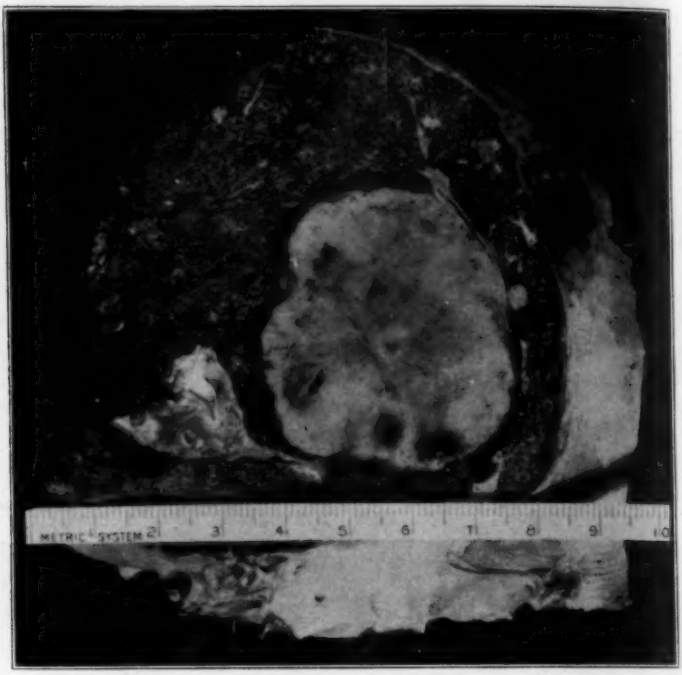

Fig. 5 (case 2).—Metastatic nodules in the liver.

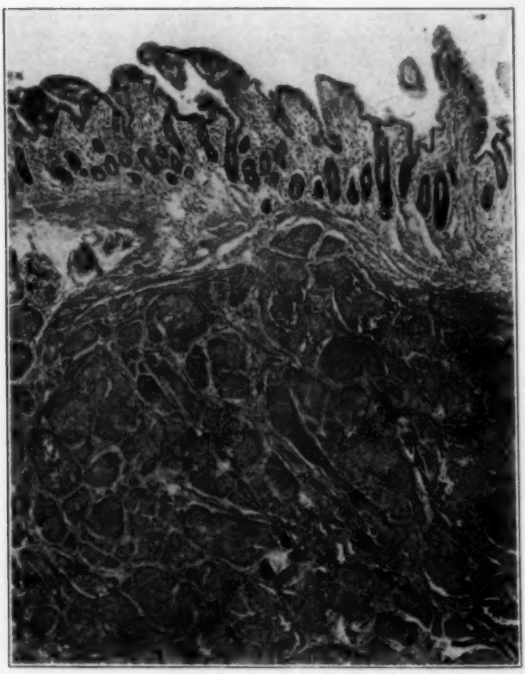

Fig. 6 (case 2).—Primary lesion of malignant carcinoid tumor of the ileum (×40).

epigastric ache. The appetite became poor. She had lost 50 pounds (22.7 Kg.) in weight during the last six months. There was a moderate amount of belching.

The patient appeared to be undernourished and anemic. The abdomen was distended and tympanitic. The edge of the liver was felt just below the costal margin. The results of examination of the urine were negative.

Exploratory operation disclosed a mass in the distal part of the ileum which produced obstruction. Other masses were found in the mesentery and on the surface of the liver. These masses were believed to be metastatic from the primary tumor in the ileum. The tumor in the ileum was removed by resection, and a side-to-side anastomosis was performed between the proximal and distal segments. In the ileum a hard, fibrous, yellowish-gray nodule 16 mm. in diameter projected into the lumen for a distance of 14 mm., producing almost complete obstruction. The nodule, on section, was found to be composed of a submucosal hard mass

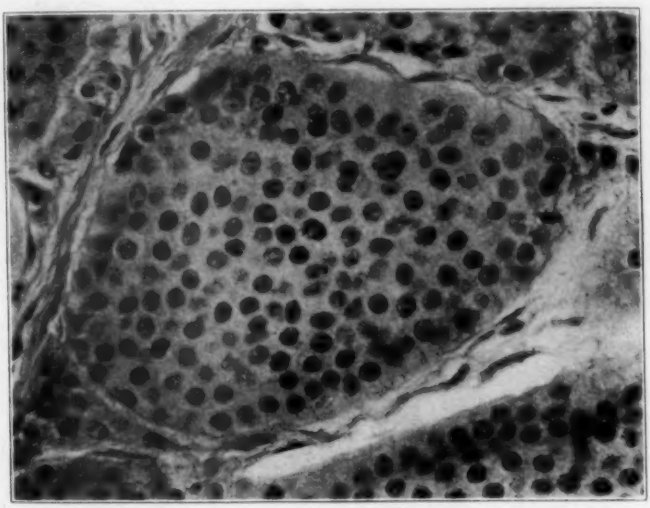

Fig. 7 (case 2).—Malignant carcinoid tumor of the ileum (× 450).

with invagination of the wall of the ileum. The serosal surface was rough, thickened and infiltrated. Five days after the operation, the wound became suppurative. The patient died fourteen days after the operation.

At necropsy a second hard, fibrous, submucosal nodule 8 mm. in diameter was found about 12 cm. from the site of the tumor which produced obstruction. The gross appearance of the two tumors was similar. The regional lymph nodes were enlarged. On section they were found to be composed of hard, yellowish tissue. In the mesentery, about 7 cm. from its attachment to the ileum, there was a hard, nodular, yellow tumor which measured 4 cm. in diameter. Underneath the capsule of the liver were numerous small, yellowish-white nodules which measured from 2 to 6 mm. in diameter. The mass which was felt on the liver at the exploratory operation and believed to be metastatic was found to be a simple cyst 6 cm. in diameter. The substance of the liver was filled with numerous small nodules from 1 to 10 mm. in diameter. In the middle of the right lobe was a sharply circumscribed, hard, yellow tumor 4.5 cm. in diameter.

The microscopic examination of sections from the primary and metastatic nodules showed the structure to be composed of the atypical epithelial cells of carcinoid tumors.

A diagnosis was made of carcinoid tumor of the ileum with metastasis to the regional lymph nodes, the mesentery, and the liver (figs. 4 to 7).

CASE 3.—*History.*—A man, aged 60, complained of hourly attacks of pain in the epigastrium. The pain radiated to the lower left quadrant of the abdomen and was followed by moderate residual discomfort. On general examination, nodular masses were found in the right and left upper quadrants of the abdomen. The systolic blood pressure was 94, and the diastolic 70, measured in millimeters of mercury. The hemoglobin was 78 per cent and the leukocytes numbered 5,800. The results of roentgen-ray examination were negative. While the patient was under observation, severe abdominal pain and general tenderness developed

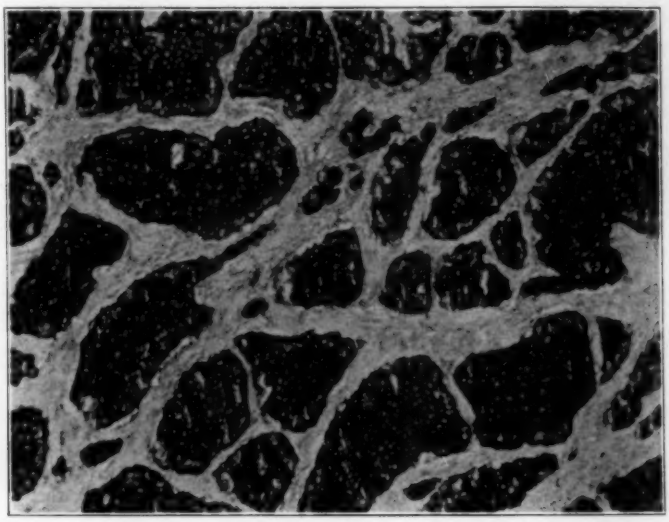

Fig. 8 (case 3).—The argentaffine reaction in the primary lesion of a malignant carcinoid tumor of the ileum (× 160).

suddenly. On exploratory laparotomy, yellow fluid was found free in the abdominal cavity. The perforation was not localized. The patient died the day after the operation.

At necropsy, multiple, firm, elevated, submucosal nodules, from 0.5 to 1.5 cm. in diameter, were found in the ileum and jejunum. At two points, the nodules appeared large enough and close enough to produce obstruction of the lumen. The ileum for a distance of 20 cm. was dilated, the wall was thickened and grayish black, and at some areas there was almost complete necrosis. The mesenteric nodules draining this region were all enlarged. At the attachment of the mesentery there was a single, hard, encapsulated mass 4.5 cm. in diameter. The cut surface of this mass was composed of compact yellowish tissue. The liver extended 7 cm. below the costal margin in the midclavicular line and weighed 3,200 Gm. On the surface were numerous yellowish, firm nodules which measured from 1 mm. to 3 cm. in diameter. On section, the liver showed many nodules from

0.5 to 6.5 cm. in diameter, scattered throughout the organ in an irregular fashion. The center of many of the larger nodules appeared somewhat soft.

Microscopic examination of the tumors in the wall of the ileum, in the mesentery and in the liver showed them to be composed of undifferentiated polygonal or round, somewhat basophilic, epithelial cells, arranged in columns, cords or irregular masses. The stroma of the tumors in the ileum was composed of bundles of smooth muscle fibers and coarse collagenous connective tissue fibers. The metastatic nodules were all definitely encapsulated. The stroma was small in amount and consisted of a few bundles of collagenous connective tissue fibers (figs. 8 and 9).

BENIGN LESIONS

CASE 4.—*History.*—A woman, aged 52, had had an attack of severe, griping, diffuse abdominal pain on Feb. 3, 1929. She was not nauseated and did not vomit.

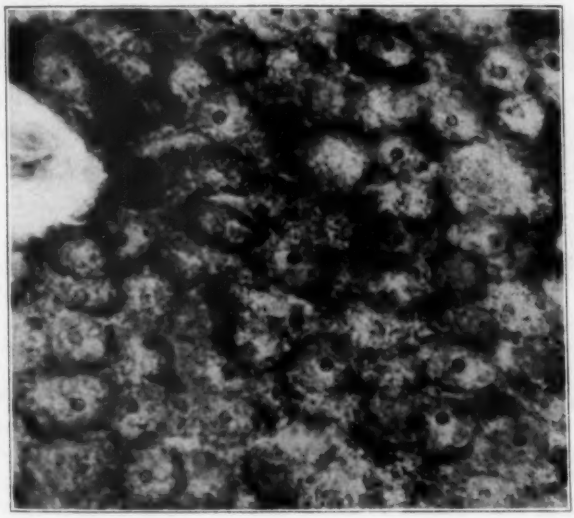

Fig. 9 (case 3).—The argentaffine granules in the cytoplasm of a malignant carcinoid tumor of the ileum (×1,200).

She weighed 200 pounds (90.7 Kg.). The abdominal wall was rigid. There was slight general abdominal tenderness. The systolic blood pressure was 125 and the diastolic 90. Complete relief followed the administration of several enemas and one hypodermic injection of morphine.

The patient was not seen again until June 29. She then had a sudden attack of severe cramplike, excruciating pain across the abdomen. The pain was slightly more marked about the umbilicus and was intermittent. Every three to four minutes it reached maximal intensity which lasted for one minute. A hypodermic injection of morphine gave relief for four hours. The pain then recurred and was associated with moderate vomiting. The vomitus was stained with bile. The hypodermic injection of morphine was repeated. The leukocytes numbered 12,000. The abdominal pain became so intense that a third injection of morphine was required four hours after the second dose. This gave relief for about twelve

hours. The bowels had not moved since the onset of the attack. A second examination of the blood showed: erythrocytes 4,300,000, leukocytes 12,400 and a negative differential count. The urine was normal.

On June 30, laparotomy was performed. There was considerable free serous fluid in the peritoneal cavity. The serosa of the small intestines appeared somewhat injected. In the ileum about 60 cm. from the ileocecal valve, there was a circular, scarlike contraction with a central lumen about 8 mm. in diameter. The ileum above this marked obstruction was definitely dilated; below it was empty and collapsed. Enlarged mesenteric lymph nodes were neither visible nor palable. The appendix and all other organs inspected appeared normal. Jejunostomy was done. The obstruction, with a small piece of adjacent intestine, was removed. The patient died about twenty-four hours after the operation, apparently from pneumonia. Necropsy was refused.

The primary tumor consisted of a firm, fibrous mass in the submucosa which encircled the lumen of the ileum. The mucosa over the upper third of the growth was ulcerated. The mass was composed of sheets, columns and masses of polyhedral cells similar to those described in case 3. In a few sections there were a number of rounded masses or clumps with a central irregular space which suggested an acinar arrangement. The largest solid masses of cells were found near the serosal surface of the tumor. There was no infiltration of leukocytes. The abundant stroma was formed by compact, interlacing, coarse bundles of collagenous fibers.

Case 5.—*History.*—A man, aged 72, had had several attacks of severe pain in the lower part of the abdomen during the last year before admission to the hospital. The pain occurred after meals and was relieved by medication. There had been marked constipation during the last year, and three weeks before examination, blood had been observed in the stools. The patient had lost 19 pounds (8.6 Kg.) in weight during the three weeks previous to admission.

A filling defect was found in the sigmoid. A clinical diagnosis of carcinoma of the sigmoid was made and a two-stage operation, for the removal of the involved portion of the colon, was performed. The patient died after the resection of an extensive carcinoma of the rectosigmoid, with involvement of the regional lymph nodes.

At necropsy, there was observed in the median portion of the ileum, a firm, circumscribed nodule 3 mm. in diameter. On microscopic examination this mass was found to be composed of atypical, polygonal or round epithelial cells, arranged in cords, columns and irregular masses. There were a few acini-like accumulations of cells. The stroma was composed of coarse collagenous fibers.

Case 6.—*History.*—A man, aged 61, had complained of dyspnea on exertion for ten years. During the last few months he had been troubled by a persistent cough. A tuberous, ulcerating mass was found on the glottis, which was diagnosed clinically as epithelioma. Two-stage laryngectomy was performed. Death from pneumonia resulted following the second stage of the operation.

A small, firm nodule 5 mm. in diameter was found at necropsy in the submucosa of the ileum, 29 cm. from the ileocecal valve. Microscopic examination of this nodule showed it to be a submucosal mass of atypical, basophilic, polygonal, epithelial cells arranged in columns and irregular masses.

Case 7.—*History.*—A man, aged 59, had had severe trigeminal neuralgia during the fifteen years previous to admission. The results of an examination were essentially negative. Death followed operation for evulsion of the sensory root of the trigeminal nerve.

At necropsy, a firm submucosal nodule, 1 cm. in diameter, was found in the ileum about 26 cm. from the ileocecal valve. On microscopic examination, the tumor was found to be composed of a number of irregular masses and sheets of atypical, basophilic, polygonal or rounded epithelial cells. Many of the cells were single or in small groups. There was no evidence of a tendency of the cells to arrange themselves in acini or acini-like formations.

CASE 8.—*History.*—A man, aged 69, had noticed gradually increasing urinary obstruction with nocturia during the six months previous to admission to the hospital. Complete retention had occurred three months previous to examination. Hypertrophy of the prostate gland was found. The patient died three days after suprapubic prostatectomy.

A hard nodule of the submucosa 3 mm. in diameter was found in the jejunum, at necropsy. The nodule was composed of atypical basophilic, epithelial cells characteristic of carcinoid tumor, arranged in columns and irregular masses.

CASE 9.—*History.*—A man, aged 58, had noticed gradually increasing intracranial pressure, beginning five months before. While he was under observation, complete right hemiplegia and aphasia developed. A clinical diagnosis of tumor of the brain was made, and a left decompression was performed. The patient died one day after the operation.

A submucosal nodule 5 mm. in diameter was found in the jejunum at necropsy. On histologic examination, the tumor was found to be composed of the characteristic carcinoid tumor cells. In some areas of the tumor there were a few small acini-like spaces, but the cells which lined these spaces did not appear identical to the atypical carcinoid tumor cells.

CASE 10.—*History.*—A man, aged 76, had noticed marked palpitation after meals for about five years. Gradually increasing symptoms of hypertrophy of the prostate gland and retention had been observed for about three years previous to admission. The general examination was essentially negative; the prostate gland was found to be enlarged, and the condition of the urine and blood was that associated with urinary retention. The patient died suddenly while he was under observation.

Two small, firm, submucosal nodules, 2 mm. in diameter were found in the ileum, at necropsy. The nodules were composed of the atypical basophilic polygonal or rounded epithelial cells characteristic of carcinoid tumors.

CASE 11.—*History.*—A man, aged 43, was attacked by a bull. He was brought to the hospital in a semicomatose condition and died soon after admission. A small, circumscribed, submucosal nodule was found in the ileum, at necropsy. On histologic examination the nodule was found to be composed of a few columns and masses of atypical polygonal, basophilic epithelial cells. The stroma was formed by a large amount of coarse connective tissue fibers and bundles of smooth muscle tissue.

STRUCTURE OF THE SMALL INTESTINE

The anatomy and general histology of the small intestine has been described by Jackson,[2] Lewis and Bremer,[3] Jordan[4] and others.

2. Jackson, C. M., in Morris: Human Anatomy, ed. 5, Philadelphia, P. Blakiston's Son & Company 1914, p. 1161.

3. Lewis, F. T., and Bremer, J. L.: Text-Book of Histology, Philadelphia, P. Blakiston's Son & Company, 1927, p. 256.

4. Jordan, H. E.: A Text-Book of Histology, ed. 3, New York, D. Appleton & Company, 1924, p. 363.

Valuable contributions to the knowledge of the embryology of the small intestine have been made by Lewis,[5] Eternod,[6] Dandy,[7] Mall,[8] Berry,[9] Carey [10] and Johnson.[11]

The intestinal glands occur throughout the entire small and large intestines. They are simple tubules which extend the whole depth of the mucous membrane and open in the small intestines between the bases of the villi. The epithelium which lines the crypts of Liberkühn consists of 3 main types of cells: goblet cells, columnar cells and cells first described by Paneth [12] that have a granular cytoplasm. The goblet cells resemble those present on the villi. The columnar cells in the deeper portions of the crypts are similar to those present on the sides of the villi. The columnar cells that line the neck of the crypts possess only an indistinct cuticular border. Mitotic figures are rather common among these cells. They are believed to be indifferent genetic cells which give rise to the various types of cells found in the intestinal glands or on the villi.

Schwalbe,[13] in 1872, was apparently the first investigator to observe the granular cells present in the intestinal glands. In his examination of the intestinal tract of the rat he described in fresh material peculiar, coarsely granular cells occupying the deeper portions of the intestinal gland. Paneth, in 1888, described a peculiar type of granular cell situated in the fundus of the intestinal glands. They were found to be present in the intestines of mice, rats, cats, dogs and man. He compared them to the pancreatic cells and distinguished them definitely from the goblet cells.

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5. Lewis, F. T.: The Development of the Intestinal Tract and Respiratory Organs, in Keibel, Franz: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 291.

6. Eternod, A. C. F.: Il y a un canal notochordal dans l'embryon humain. Anat. Anz. **16**:131, 1899.

7. Dandy, W. E.: A Human Embryo With Seven Pairs of Somites, Am. J. Anat. **10**:85, 1910.

8. Mall, F. P.: Ueber die Entwickelung des menschlichen Darmes und seiner Lage beim Erwachsenen, Arch. f. Anat. u. Entwicklungsgesch. supp. 2, p. 403, 1897: Development of the Human Intestine and Its Position in the Adult, Bull. Johns Hopkins Hosp. **9**:197, 1898.

9. Berry, J. M.: On the Development of the Villi of the Human Intestine. Anat. Anz. **17**:242, 1900.

10. Carey, E. J.: Studies on the Structure and Function of the Small Intestine. Anat. Rec. **21**:189, 1921.

11. Johnson, F. P.: The Development of the Mucous Membrane of the Oesophagus, Stomach, and Small Intestine in the Human Embryo, Am. J. Anat. **10**:521, 1910.

12. Paneth, Josef: Ueber die secernierenden Zellen des Dünndarmepithels, Arch. f. mikr. Anat. **31**:113, 1888.

13. Schwalbe, C.: Beitrage zur Kenntnis der Drüsen in den Darmwandungen insbesondere der Brunner'schen Drüsen, Arch. f. mikr. Anat. **8**:92, 1872.

Kultschitzky,[14] in 1897, described a granular cell observed in the intestinal mucosa of dogs. The granules took a red color when stained by Ehrlich-Biondi solution. Since the granules took an acid stain, he named them "Zellen mit azidophilen Körnern." The intestinal tract of dogs on their usual diet contains a moderate number of these cells; they increase when the animals are put on an abundant meat diet and decrease in number and size on starvation. Schmidt,[15] in 1905, described the presence of certain granular cells in the mucous membrane of the intestines of human beings. He fixed his material in Müller-formaldehyde solution. In both stained and unstained preparations, he observed peculiar cells which contained numerous yellow granules in their basal portions. He believed these cells to be of a different type from those described by Paneth and Kultschitzky. On the basis of the yellow granulation he called the cells "gelbe Zellen." Ciaccio[16] shortly afterward described a special granular cell in the crypts of Lieberkühn. The cells were investigated only in guinea-pigs and dogs. Besides the granules, numerous vacuoles were found in the cytoplasm. Klein[17] examined the granule cells of the opossum and guinea-pig. He reached the conclusion that they are specific elements which secrete a special substance used during digestion. The granules were found to vary in size and shape. The smaller granules take a basic stain, and the larger, coarser granules are acidophilic.

Gosset and Masson[18] restudied the granular cells of the intestinal mucosa. As a stain they used a solution of ammoniacal silver. In the deeper portions of the intestinal glands and in the region adjacent to the crypts, peculiar cells were found. Between the basement membrane and nucleus were numerous silver-staining granules of various sizes. The cells which contained these granules were called argentaffine cells. The cells were regarded as composing an endocrine gland of entodermal origin comparable to the islands of Langerhans of the pancreas. On proliferation the argentaffine cells formed an organoid tissue. The presence of silver-reducing cytoplasmic granules in the

14. Kultschitzky, N.: Zur Frage über den Bau des Darmkanals, Arch. f. mikr. Anat. **49**:7, 1897.

15. Schmidt, J. E.: Beiträge zur normalen und pathologischen Histologie einiger Zellerten der Schleimhaut des menschlichen Darmkanals, Arch. f. mikr. Anat. **66**:12, 1905.

16. Ciaccio, Carmelo: Sur une nouvelle espèce cellulaire dans les glandes de Lieberkühn, Compt. rend. Soc. de biol. **60**:76 (Jan. 13) 1906.

17. Klein, Sidney: On the Nature of the Granule Cells of Paneth in the Intestinal Glands of Mammals, Am. J. Anat. **5**:315, 1906.

18. Gosset, A., and Masson, P.: Tumeurs endocrines de l'appendice, Presse méd. **25**:237, 1914.

cells of the intestinal glands has been confirmed by Hasegawa,[19] Danisch,[20] Sprafke [21] and other investigators.

Kull [22] in the examination of the intestines of human beings, observed several types of granular cells. He classified these into: (1) Paneth's cells, (2) cells with fine basal oxyphilic granules (the "acidophilen Zellen") and (3) cells with coarse yellowish basal granules (the "gelben Zellen" of Schmidt), which he considered as chromaffin cells.

Masson,[23] in 1924, investigated in detail the argentaffine cells of the appendix, but did not contribute new data. Cordier [24] found that the granule cells in the intestinal glands of guinea-pigs decreased or disappeared after the subcutaneous injection of pilocarpine hydrochloride. The granules in the pancreatic acini-like spaces were also diminished in number. In one hour and fifteen minutes after the injection, the granules had reappeared in the cells. The conclusion was reached that these cells have a secretory function similar to that of the pancreatic cells. Kull,[25] in a recent histologic and embryologic study of the granule cells of the intestinal tract, reached the conclusion that the granule cells are of mesodermal origin. Various color reactions of the granules in various cells are believed to be an index of development. Acidophilic granules are considered present only in young cells, whereas yellow granules are evidence of cell maturity. The size and number of the granules are a direct expression of the functional activity of the cells.

REVIEW OF THE LITERATURE

Carcinoid tumors of the small intestine usually appear as small, circumscribed, firm nodules which project into the lumen. They are often multiple. The color varies with their size and tension on the superimposed mucosa. The larger nodules are yellow to grayish white. Their size varies from 3 mm. to 1 cm. or more in diameter. Their free surfaces are usually covered by the smooth normal mucosa, but

19. Hasegawa, Tomoo: Ueber die Carcinoide des Wurmfortsatzes und des Dünndarmes, Arch. f. path. Anat. **244**:8, 1923.

20. Danisch, Felix: Zur Histogenese der sogennanten Appendixkarzinoide, Beitr. z. path. Anat. u. z. allg. Path. **72**:687, 1923.

21. Sprafke, Hans: Untersuchungen über die argentaffinen Zellen in der Schleimhaut des Wurmfortsatzes und ihre Beziehungen zur Enstehung der sogenannten Karzinoide, Frankfurt. Ztschr. f. Path. **35**:302, 1927.

22. Kull, Harry: Die "basal gekörnten Zellen" des Dünndarmepithels, Arch. f. mikr. Anat. **81**:185, 1913.

23. Masson, P.: Appendicite neurogene et carcinoides, Ann. d'anat. path. **1**:3, 1924.

24. Cordier, Robert: Contribution à l'étude de la cellule de Ciaccio-Masson et de la cellule de Paneth, Compt. rend. Soc. de biol. **88**:1227 (April 28) 1923.

25. Kull, Harry: Die chromaffinen Zellen des Verdauungstraktes, Ztschr. f. mikr.-anat. Forsch. **2**:163, 1925.

there may be superficial erosions or ulcerations which may produce irregular crater-like depressions. The primary nodules have the consistence of a hard fibroma. On section the surface is yellowish and firm. The histologic structure consists of irregularly arranged strands, columns and masses of peculiar polyhedral cells in an abundant, compact stroma of coarse collagenous fibers or bundles of smooth muscle.

Various names have been applied to carcinoid tumors of the small intestines. Many investigators, in their desire to emphasize a hypothetic histogenesis, have renamed these tumors. Langhans,[26] in 1867, described the first case as a polyp. Lubarsch,[27] in 1888, and Ransom,[28] in 1890, believed them to be atypical primary carcinomas and used the term carcinomata. Oberndorfer,[29] in 1907, was the first to use the term carcinoid to emphasize certain characteristics by which this tumor differed from true carcinoma. Bunting,[30] in 1904, Burckhardt,[31] in 1909, and Krompecher,[32] in 1919, used the term basel-cell carcinoma or basiloma to call attention to the morphologic resemblance of carcinoid tumors to basal cell carcinoma. Other recent terms are embryoma, by Primrose [33] in 1925, immature sympathetic neurocytomata, by Ehrlich [34] in 1914, argentaffine tumor, by Gosset and Masson [18] in 1914, endocrine tumor, by Masson [23] in 1924 and neurocrine tumor, by Masson [35] in 1928.

Carcinoid tumors may occur anywhere in the gastro-intestinal tract. They are most common in the appendix and the small intestines. Saltykow [36] described tumors in the sigmoid and rectum composed of carcinoid cells.

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26. Langhans, T.: Ueber einen Drüsenpolyp im Ileum, Arch. f. path. Anat. **38**:559, 1867.

27. Lubarsch, Otto: Ueber den primären Krebs des Ileum nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberculose, Virchows Arch. f. path. Anat. **111**:281, 1888.

28. Ransom, W. B.: Primary Carcinoma of the Ileum, Lancet **2**:1020, 1890.

29. Oberndorfer, Siegfried: Ueber die "kleinen Dünndarmcarcinome," Verhandl. d. deutsch. path. Gesellsch. **11**:113, 1907.

30. Bunting, C. H.: Multiple Primary Carcinomata of the Ileum, Bull. Johns Hopkins Hosp. **15**:389 (Dec.) 1904.

31. Burckhardt, J. L.: Zur Lehre der kleinen Dünndarmkarzinome, Frankfurt. Ztschr. f. Path. **3**:593, 1909.

32. Krompecher, E.: Über die Basalzellentumoren der Zylinderepithelschleimhäute mit besonderer Berücksichtigung der „Karzinoid" des Darms, Beitr. z. path. Anat. u. z. allg. Path. **65**:79, 1919.

33. Primrose, Alexander: Primary Carcinoma of the Small Intestine in an Octogenarian, Ann. Surg. **82**:429, 1925.

34. Ehrlich, S. L., quoted by Masson, P.: Am. J. Path. **4**:181, 1928.

35. Masson, P.: Carcinoids (Argentaffin-Cell Tumors) and Nerve Hyperplasia of the Appendicular Mucosa, Am. J. Path. **4**:181 (May) 1928.

36. Saltykow, S.: Ueber die Genese der "karsinoiden Tumoren" sowie der "Adenomyome" des Darmes, Beitr. z. path. Anat. u. z. allg. Path. **54**:559, 1912.

More than 104 cases of carcinoid tumors of the small intestines are reported in the literature. About 8 cases could not be considered on account of a meager or inconclusive description. A few reports of

Cases of Carcinoid Tumor of Small Intestines Reported in the Literature

Author	Year Reported	Metastasis to the Liver and Other Structures	Metastasis to the Lymph Nodes	Cases	Extension to the Serosa
Langhans	1867	..	..	1	..
Lubarsch	1888	..	..	2	..
Ransom	1890	1	..	1	..
Notthafft: Deutsches Arch. f. klin. Med. **54:** 555, 1895	1895	..	..	1	..
Walter: Arch. f. klin. Chir. **53:** 1, 1896	1896	..	..	1	..
Oberndorfer: Beitr. z. path. Anat. u. z. allg. Path. **29:** 519, 1901	1901	..	..	2	..
Grawitz: Deutsche med. Wchnschr. **30:** 1794 (Dec. 1) 1904	1904	..	..	1	..
Bunting	1904	..	..	1	..
Marckwald: München. med. Wchnschr. **1:** 1033 (May 30) 1905	1905	..	..	1	..
Oberndorfer[29]	1907	..	..	5	..
Trappe: Frankfurt. Ztschr. f. Path. **1:** 109, 1907	1907	..	..	1	..
Versé: quoted by Burckhardt [31]	1908	..	1*	3	2†
Versé: Verhandl. d. deutsch. path. Gesellsch. **12:** 95, 1908	1908	..	..	6	..
Burckhardt [31]	1909	..	..	6	..
Toenniessen: Ztschr. f. Krebsforsch. **8:** 354, 1910	1910	..	..	11	..
Evstratoff: Schweiz. ärztl. Mitt. a. Univ.-Inst., Zürich **7:** 301, 1911	1911	1	..	1	..
Saltykow	1912	..	1‡	5	..
Burckhardt: Frankfurt. Ztschr. f. Path. **11:** 219, 1912	1912	..	..	1	..
Gruner and Fraser: J. Path. & Bact. **17:** 165, 1912	1912	..	..	2	..
Dietrich: Frankfurt. Ztschr. f. Path. **13:** 390, 1913	1913	1	..	1	..
Schopper: Verhandl. d. deutsch. path. Gesellsch. **16:** 387, 1913	1913	1	..	1	..
Hageman: Ztschr. f. Krebsforsch. **16:** 404, 1917	1917	..	..	10	..
Judd: Journal-Lancet **39:** 159 (April 1) 1919	1919	..	..	2	..
Engel: Ztschr. f. ang. Anat. **7:** 385, 1920	1920	..	1	1	..
Bakke: Med. Rev. **38:** 193, 1921	1921	..	1	1	..
Schnebel: Arch. f. klin. Chir. **124:** 652, 1923	1923	1	..	1	..
Hasegawa	1923	..	..	4	1
Lauche: Virchows Arch. f. path. Anat. **252:** 38, 1924	1924	..	..	2	..
Primrose	1925	..	..	1	..
Liu: Arch. Surg. **11:** 602 (Oct.) 1925	1925	..	1	1	..
Forbus: Bull. Johns Hopkins Hosp. **37:** 130, 1925	1925	..	..	2	..
Stewart and Taylor: J. Path. & Bact. **29:** 135, 1926	1926	..	..	1	..
Dukes and Lockhart-Mummery: J. Path. & Bact. **29:** 308, 1926	1926	1	..	1	..
Heine: Deutsche Ztschr. f. Chir. **205:** 126, 1927	1927	..	..	1	..
Huguier: Paris chir. **19:** 38 (Jan.) 1927	1927	..	..	1	..
Windholz: Frankfurt. Ztschr. f. Path. **35:** 422, 1927	1927	..	..	1	..
McGlannon and McCleary: J. A. M. A. **89:** 850 (Sept. 10) 1927	1927	..	..	1	..
Decker: Rev. méd. de la Suisse Rom. **48:** 145, 1928	1928	..	1	1	..
Brocher: Rev. méd. de la Suisse Rom. **48:** 50, 1928	1928	1	..	3	..
Semsroth: Arch. Path. **6:** 575 (Oct.) 1928	1928	..	..	1	..
Thibaudeau: J. Cancer Research **13:** 66 (March) 1929	1929	..	..	1	..
Oberndorfer: In Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 4, p. 717	1929	1	4	13	..
Total		8	10	104	3

* Case IX. † Cases III and VII. ‡ Case VII.

cases were not available. The cases used as the basis for this summary are definite, microscopically proved cases of carcinoid tumors of the small intestines (table). They are composed of 21 malignant and 83 benign neoplasms.

For the sake of ready analysis, the 21 malignant cases will be considered in 3 groups. The first group includes 8 cases in which there was general metastasis, the second group includes 10 cases in which there was metastasis to the regional lymph nodes, and the third group consists of 3 cases in which the growth extended through the intestinal wall to involve the serosa.

The Malignant Lesions.—In the twenty-one cases of malignant carcinoid tumor of the small intestine, the patients consisted of twelve men and eight women; in 1 case, the sex of the patient is not known. The patients between the ages of 30 and 40 consisted of one man and one woman; between 41 and 50, four men; between 51 and 60, five men and two women; between 61 and 70, one man and two women; between 71 and 80, one man and two women, and between 81 and 90, a woman. In one case the age of the patient is not known. The average age in the twenty malignant cases was 57.2 years; the average age for the men was 53.2 years, and for the women 61.3 years.

The primary lesion was in the ileum in all 21 cases; it was in the upper portion in 3 cases, in the middle portion in 1 case, and in the lower portion in 17 cases. Four of these 17 tumors were within 10 cm. of the ileocecal valve. The smallest primary lesion was 5 mm. in diameter, and the largest 4 cm. in diameter.

In 17 cases the primary growth was nodular; in 4 cases it was annular. The primary lesion was multiple in 8 cases and single in 11 cases. In 4 cases in which the number of multiple nodules was recorded they numbered 14, 2, 14, and 10. In 10 cases there were symptoms and signs typical of obstruction in the small intestine. In 2 cases there were indefinite complaints of cachexia and anemia.

The Benign Lesions.—In 83 cases regional or distal metastasis was not found. The neoplasm did not involve the serosa. This group will be considered as benign to distinguish it from the previously described group in which metastasis had occurred. The amount of published data varies considerably in the different reports. This summary cannot, therefore, include every case in the consideration of the various factors. In 73 cases, the patients included 38 men and 35 women.

The age distribution in 68 cases (forty men and twenty-nine women) was as follows: The youngest man was aged 33 and the youngest woman, 20; the oldest man was 86 and the oldest woman 79. The average age in 68 cases was 54.3 years; the average age for the twenty-eight women, 47 years and for the forty men, 58.8 years. The patients between the ages of 20 and 30 included five women; between 31 and 40, three men and seven women; between 41 and 50, six men and four women; between 51 and 60, eleven men and three

women; between 61 and 70, ten men and seven women; between 71 and 80, seven men and one woman, and between 81 and 90, three men and one woman.

In 71 cases, the lesion was situated as follows: in the duodenum in 2 cases, in the upper portion in 1 case, and the site was not designated in 1 case; it was situated in the jejunum in 11 cases, and in the ileum in 58 cases; in the upper portion in 7 cases, in the middle portion in 5 cases, in the lower portion in 44 cases and in the tip of a Meckel's diverticulum in 2 cases.

The number of nodules varied from 1 to 33 in 76 cases; single nodules occurred in 49 cases, and multiple nodules were found in 27 cases. In the 27 cases there were from 1 to 5 nodules in 16 cases; from 6 to 10 nodules in 3 cases; 24 nodules in 1 case; 33 nodules in 1 case and multiple nodules, but the number was not given, in 6 cases. The lesions were nodular in 62 of 63 cases and ring-shaped in 1. The size of the nodules varied from 1 mm. to 2.5 cm. in diameter. The usual diameter was from 3 to 8 mm.

Of the 83 cases, 6 were discovered at exploratory operation and 75 at necropsy; in 2 cases these data are absent. The symptoms in the 6 cases were typical of intestinal obstruction.

Histogenesis.—The histogenesis of carcinoid tumors has been a subject of much discussion during the last thirty years. There are many factors that have stimulated continuous interest in this group of tumors. It is sufficient to call attention to a few, such as the atypical cytologic manifestations, small size, unusual distribution, multiplicity and variable clinical course. Many cell types from all germ layers and a number of embryonic anomalies have been considered as the origin of the tumor. Although much intensive work has been done, a theory of histogenesis has not been generally accepted. The application of the chrome fixatives and silver stains in the differentiation of the cells, however, has resulted in considerable elucidation of this problem.

The various conceptions of the origin of the tumor will first be tabulated for easy reference, and then considered in detail.

I. Cells which form the crypts of Lieberkühn.
  1. Cell type not designated [37]
  2. Cell similar to the basal cells of the epidermis [38]

37. Langhans (footnote 26). Lubarsch (footnote 27). Walter, Maximilian: Ueber das multiple Auftreten primären bösartigen Neoplasmen, Arch. f. klin. Chir. **53**:1, 1896. Gruner, O. C., and Fraser, J. R.: Primary Carcinoma of the Ileum, J. Path. & Bact. **17**:165, 1912. Schopper, K. I.: Ueber ein "kleines Dünndarmkarzinom" mit ausgedehnter Metastasebildung, Verhandl. d. deutsch. path. Gesellsch. **16**:387, 1913.

38. Bunting (footnote 30). Krompecher (footnote 32). Burckhardt, J. L.: Ueber das kleine Dünndarm- und Appendix-Karzinom, Frankfurt. Ztschr. f. Path. **11**:219, 1912.

3. Granular cells
   (*a*) Paneth's cells [39]
   (*b*) Chromaffin cells [40]
   (*c*) Argentaffine cells [41]

II. Pancreatic tissue
   1. Pancreatic tissue displaced during fetal life [42]
   2. Pancreatic tissue (islands of Langerhans [43])

III. Sympathetic nervous system
   1. Cells of the celiac ganglia [20]
   2. Cells of Auerbach's plexus [34]

IV. Embryonic maldevelopments
   1. Embryonic remnants of the ductus omphalomesentericus [44]
   2. Embryonic epithelial rests [45]
   3. Embryonic heterotopic tissue [46]
   4. Faulty differentiation of the entoderm [47]

The peculiar morphologic appearance of the characteristic cells that compose carcinoid tumors impressed even the earliest observers. The microscopic distinction from adenocarcinoma of the small intestine is

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39. Huebschmann, P.: Sur le carcinome primitif de l'appendice vermiculaire, Rev. méd. de la Suisse Rom. **30**:317, 1910.

40. Dukes, Cuthbert, and Lockhart-Mummery, P.: Carcinoid Tumour of the Ileum with Metastases, J. Path. & Bact. **29**:308, 1926. McGlannon, Alexius; and McCleary, Standish: Carcinoid Tumors of the Small Intestines, J. A. M. A. **89**:850 (Sept. 10) 1927. Huebschmann (footnote 39).

41. Gosset and Masson (footnote 18). Hasegawa (footnote 19). Sprafke (footnote 21). Masson (footnotes 23 and 35). Forbus, W. D.: Argentaffine Tumors of the Appendix and Small Intestine, Bull. Johns Hopkins Hosp. **37**:130, 1925.

42. Trappe, Max: Ueber geschwülstartige Fehlbildungen von Niere, Milz, Haut und Darm, Frankfurt. Ztschr. f. Path. **1**:109, 1907. Dietrich, A.: Kleine Darmkarzinome von Typus der Karzinoide mit schwerer Leberkarzinose, Frankfurt. Ztschr. f. Path. **13**:390, 1913. Oberndorfer, Siegfried: Die Geschwülste des Darmes, in Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 4, p. 717. Heller, A.: Discussion, Verhandl. d. deutsch. path. Gesellsch. **11**:115, 1907.

43. Saltykow (footnote 36). Lauche, Arnold: Die Heterotopien des ortsgehörigen Epithels im Bereich des Verfauungskanals, Virchows Arch. f. path. Anat. **252**:38, 1924.

44. Marchand, F.: Discussion, Verhandl. d. deutsch. path. Gesellsch. **11**:115, 1907. Sternberg, C.: Discussion, Verhandl. d. deutsch. path. Gesellsch. **11**:116, 1907.

45. Toenniessen, E.: Untersuchungen über die in der Submukosa des Dünndarms vorkommenden epithelialen Tumoren, Ztschr. f. Krebforsch. **8**:354, 1910. Borrmann, R.: Discussion, Verhandl. d. deutsch. path. Gesellsch. **11**:116, 1907.

46. Hageman, F.: Ueber die Beiziehungen der sogennanten Karzinoide des Darms zu den Darmkrebsen, Ztschr. f. Krebforsch. **16**:404, 1917.

47. Semsroth, Kurt: The Histogenetic Interpretation of Certain Carcinoids of the Small Intestines, Arch. Path. **6**:575 (Oct.) 1928.

easy and definite. Langhans, who first described the carcinoid tumors of the small intestine, emphasized the unusual appearance of the polyhedral cells. It was his belief that the origin of the cells was directly from the epithelial cells of the crypts of Lieberkühn. Lubarsch described the arrangement of the cells in nests and strands. He emphasized the dissimilarity between the cells that composed these tumors and the cells that formed ordinary adenocarcinoma. He demonstrated by serial sections direct connection between the strands of carcinoid cells and the crypts of Lieberkühn. He concluded that the tumors differed from adenocarcinoma or any other previously described neoplasm of the gastro-intestinal tract. As the basis for this distinction, he called attention to the multiplicity of the tumor, lack of metastasis, absence of true glands, gross appearance and peculiar structure of the individual cells. The epithelial cells of the glands of Lieberkühn were believed to be the type cell. By calling the tumor "primary carcinoma of the ileum," he failed to impress the distinction from adenocarcinoma which he had made. The majority of observers during the next ten years [48] accepted Lubarsch's histogenic conception. Bunting in 1904, Burckhardt in 1909, and Krompecher in 1919, suggested, on account of the morphologic resemblance, that carcinoid tumors were similar to basal cell carcinoma.

Krompecher [32] suggested that the basal cells of Lieberkühn's crypts can differentiate into any of three types of basal cell carcinoma. These types he designated as solid, cystic and adenomatous basal cell carcinoma. He did not furnish any report of a case of carcinoid tumor.

Huebschmann, in 1910, in his study of carcinoid tumors of the appendix, made the suggestion that on account of the yellow color of these neoplasms they originated from Paneth's cells or from the chromaffin cells. He did not use chromic acid as a fixative. McGlannon and McCleary examined a carcinoid tumor that they believed to originate from the chromaffin cells at the base of the crypts of Lieberkühn. The cytoplasmic granules gave a difinite argentaffine reaction. Dukes and Lockhart-Mummery, in a thorough histologic study, reached the same conclusions.

Gosset and Masson, in 1914, studied the chromaffin cells of the intestinal tract, and were the first to show that cytoplasmic granules, present in certain cells situated at the base of the crypts of Lieberkühn, reduced an ammoniacal solution of silver salts. The granules were stained black. A new nomenclature was suggested by this reaction. The granules were called argentaffine granules, the cells in which the

48. Notthafft, A.: Ueber die Entstehung der Carcinome, Deutsches Arch. f. klin. Med. **54**:555, 1895. Walter (footnote 37, third reference). Gruner and Fraser (footnote 37, fourth reference). Schopper (footnote 37, fifth reference).

granules were found, argentaffine cells, and tumors which were partly or wholly formed by these cells, argentaffine tumors. Significant observations were made on the argentaffine cells. They were found in the deeper portions of the crypts of Lieberkühn throughout the entire gastro-intestinal tract. Most of them were found between the cylindric cells of the mucosa, but an occasional cell was not in direct contact with the lumen. The cells were believed to form an endocrine gland of endodemic origin similar to the islands of Langerhans. On proliferation of certain argentaffine (neurocrine) cells, a tissue was formed which was believed to possess an organoid character. Danisch, Hasegawa, and Forbus substantiated the presence of argentaffine cells in the crypts of Lieberkühn. Forbus used the argentaffine reaction as a means of distinguishing carcinoid tumors of the small intestine from other growths. He was of the opinion that unless the cells of a morphologically carcinoid tumor show the argentaffine reaction, it should be considered as an adenocarcinoma. By this means he suggested the possibility of differentiating a third group of epithelial intestinal neoplasms which has the microscopic morphology of carcinoid tumor but the clinical course of adenocarcinoma. Hasegawa concluded that carcinoid tumors of the small intestines may arise in three different ways: (1) directly from the principal cells of the crypts of Lieberkühn, (2) from the chromaffin cells and (3) from the submucous epithelial rests. Masson,[49] in his later work based on the study of fifty carcinoid tumors from the appendix, concluded that the argentaffine cells migrate from the crypts of Lieberkühn into the submucosa. Here the cells invade a mass of subglandular nonmedullated nerve fibers. In this situation, the cells may differentiate into any 1 of 4 types: (1) cylindrical, (2) ganglionic, (3) resembling Schwann's and (4) neurocrine. Carcinoid tumors originate by autonomous amitotic division of the neurocrine cells. On proliferation, the neurocrine cells rupture the nerve sheaths and extend into the submucosa.

Danisch, on the basis of embryologic observations, came to a somewhat different conclusion. He observed that argentaffine cells do not appear in the crypts of Lieberkühn until the fourth fetal month. He did, however, see the argentaffine cells in the submucosal connective tissue of the intestines in an 11.5 cm. human embryo. Here the argentaffine cells were not in relation to the already well developed crypts of Lieberkühn, but were situated as individual cells in the loose connective tissue. The cells were believed to migrate from the connective tissue into the crypts of Lieberkühn. By studies on the chick embryo, he found that argentaffine cells first appear in the celiac ganglion. He concluded that argentaffine cells originating in the celiac ganglion migrated

49. Masson (footnotes 23 and 35).

along the nerve fibers into the submucosa and eventually reached the crypts of Lieberkühn. If argentaffine cells remained about Meissner's ganglions or in the submucosa, they could form carcinoid tumors. The origin of carcinoid neoplasms is thus paraganglionic, from the celiac ganglion of the sympathetic system. Masson [35] and Danisch agreed that the type cell of carcinoid tumors is from argentaffine cells present in the submucosa. Masson,[49] however, suggested the crypts of Lieberkühn or the endoderm, and Danisch pointed out the chromaffin cells of the sympathetic ganglion or the ectoderm as the actual source of the argentaffine cells.

Ehrlich stated that carcinoid tumors arise from Auerbach's plexus. The tumor cells would thus originate from sympathetic nerve cells. He designated the tumors as immature sympathetic neurocytomata.

Oberndorfer, in 1907,[50] presented his work on carcinoid tumors of the small intestine, based on the examination of 6 cases of benign tumors. He directed attention to several characteristics of these tumors which have become widely accepted. The tumors were described as small, usually multiple, circumscribed, submucosal, noninfiltrating, benign masses of undifferentiated cells. To distinguish the clinical course from that of carcinoma, he suggested the name carcinoid tumor. A definite statement was not made as to the origin, but he seemed to favor the possibility that they are derived from pancreatic rests. Trappe, in 1907, suggested that rests of pancreatic tissue are common in the gastro-intestinal tract. These rests were considered by him to be the source of carcinoid tumors and adenomyomas of the small intestine. Heller and Albrecht [51] supported the opinion of Trappe.

Saltykow developed the ideas of Trappe still further. He expressed the belief that carcinoid tumors originate from rests composed entirely of islands of Langerhans. Lauche also considered this to be the most plausible explanation of their true nature.

Marchand and Sternberg expressed the belief that the carcinoid tumor develops from cellular remnants of the ductus omphalomesentericus.

Embryonic epithelial rests were first suggested as the origin of carcinoid tumors by Borrmann. Toenniessen considered them not only as derived from submucosal epithelial rests, but suggested that they might function as glands of internal secretion. The similarity of the carcinoid cells and the cells of the islands of Langerhans was emphasized by him as additional proof.

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50. Oberndorfer (footnote 42, third reference).

51. Albrecht, H.: Discussion, Verhandl. d. deutsch. path. Gesellsch. **11**:115, 1907.

Hageman presented in considerable detail his conception of the development of carcinoid tumors from embryonic heterotopic tissue present in the intestinal wall.

Semsroth, in 1928, suggested that carcinoid tumors in the duodenum develop as the result of dysontogenetic heterotopy. This conclusion was reached on the observations in one case in which there was no sign of malignancy, but evidence of dysotogenesis in the form of pancretatic tissue in the duodenum. Kull [25] expressed the belief that the argentaffine cells originate from cells in the submucosa which migrate into the crypts of Lieberkühn. This conception of the origin of the argentaffine cells suggests a possible mesodermal type cell to be the progenitor of carcinoid tumors.

In summarizing the conception of the histogenesis of carcinoid tumors, it is apparent that at present there are a number of possibilities, none of which can be considered as proved or established. The origin of carcinoid tumors has been assigned to the principal epithelial cells of the crypts of Lieberkühn, to Paneth's cells and to the basal granular cells (chromaffin cells). They have been considered malformations developing from pancreatic rests or accessory pancreas, and finally as fetal epithelial rests or remnants of the ductus omphalomesentericus.

COMPARISON WITH BASAL CELL CARCINOMA OF THE SKIN

There are certain resemblances between carcinoid tumors of the small intestine and basal cell carcinoma of the skin that have led some investigators to believe that these tumors are related.[31] The cells of both tumors take a basic stain, they tend to grow in solid sheets or cords and do not show cell boundaries. The benign clinical course of both was emphasized before it was recognized that many carcinoid tumors of the intestine form metastasis. However, a close histologic study revealed wide differences in structure. Basal cell carcinomas frequently show a few cornified cells, and they never give the argentaffine reaction. In 268 cases of basal cell carcinoma, Broders [52] did not find metastasis beyond the regional nodes.

COMPARISON WITH CARCINOID TUMORS OF THE VERMIFORM APPENDIX

Selinger stated that the first case of authentic carcinoid tumor of the appendix was reported by Beger [53] in 1882. Up to 1906, only 42

52. Broders, A. C.: Basal-Cell Epithelioma, J. A. M. A. **72**:856 (March 22) 1919.

53. Beger, A.: Ein Fall von Krebs des Wurmfortsatzes, Berl. klin. Wchnschr. **19**:616 (Oct.) 1882.

cases had been reported. Simon,[54] in 1916, in a careful examination of the literature, found 325 cases of epithelial tumors of the appendix. After excluding all cases of apparent adenocarcinoma and doubtful cases, he concluded that 260 were of definite carcinoid type. Van Alstine[55] reviewed 300 cases in 1926, and Oberndorfer, in 1929, described 29 cases observed in his own laboratory.

Carcinoid tumors of the appendix are more common than carcinoid tumors of the small intestines. Warwick[56] found in statistics of 29,320 appendixes removed at operation, that in 82 (0.28 per cent) carcinomatous tumors were present. Kennedy[57] examined 350 appendixes removed at necropsy, but found only one case (0.28 per cent) of carcinoma. In a study of 41,838 necropsies, Maydil and Nothnagel[58] observed 2 cases of carcinoma of the appendix. Reimann[59] found 17 cases of carcinoma on examination of 13,151 appendixes removed at operation. Three of the 17 cases were of the columnar cell type whereas 14 (82 per cent) were carcinoid in structure. MacCarty and McGrath,[60] in the examination of 8,039 appendixes as a routine, found 40 cases of carcinoma.

MacCarty and McGrath noted that the average age of the 40 patients with carcinoma of the appendix was 30 years. Oberndorfer[50] reported that in 11 cases of carcinoid tumors discovered at necropsy the average age was 57 years, whereas in 18 cases discovered in surgically removed specimens the average age was 24 years. In 66 per cent of 186 cases of carcinoid tumors of the appendix Simon found that the patients were less than 30 years. Selinger[61] found that the average age of the patients in 34 cases of primary carcinoma of the appendix was 34 years.

The majority of reported cases has occurred in women. MacCarty and McGrath found 24 per cent in males and 76 per cent in females; Selinger found 17.6 per cent in males and 82.4 per cent in females; Simon found 34.9 per cent in males and 65.1 per cent in females, and Oberndorfer[50] found 29 per cent in males and 61 per cent in females.

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54. Simon, W. V.: Das Karzinom und das Karzinoid der Appendix mit einem kurzen Überblick auch über die übrigen an der Appendix vorkommenden Tumoren, Ergebn. d. Chir. u. Orthop. **9**:291, 1916.

55. Van Alstine, G. S.: Primary Carcinoma of the Appendix: Report of Two Cases with Brief Review of the Literature, Illinois M. J. **49**:469 (June) 1926.

56. Warwick, Margaret: Primary Carcinoma of the Appendix, Minnesota Med. **5**:512, 1922.

57. Kennedy, A. M.: Primary Carcinoma of Appendix, Lancet **2**:1757, 1910.

58. Maydil and Nothnagel, quoted by Whipham, T. R. C.: Lancet **1**:319, 1901.

59. Reimann, S. P.: Primary Carcinoma of the Vermiform Appendix, Am. J. M. Sc. **156**:190, 1918.

60. MacCarty, W. C., and McGrath, B. F.: The Frequency of Carcinoma of the Appendix, Ann. Surg. **59**:675, 1914.

61. Selinger, J.: Primary Carcinoma of the Vermiform Appendix, Ann. Surg. **89**:276 (Feb.) 1929.

Carcinoid tumors of the appendix are most commonly situated in its distal third. Simon found 139 cases distributed as follows: in the distal third, 77 per cent; in the middle third, 14 per cent; in the upper third, 7 per cent and in the entire organ, 2 per cent.

MacCarty and McGrath found in 40 cases that 90 per cent were situated at the tip. Reimann stated that in 17 cases of carcinoma of the appendix, "practically all of the tumors were situated at the tip or in the distal third. A bulbous tip was exhibited by four." Selinger described the situation of the lesion in 34 cases as follows: "twenty at the tip, five at the base, one midway between tip and base."

Carcinoid tumors of the appendix consist almost always of a single nodule. Simon stated that only 5 cases of multiple carcinoid tumors of the appendix had been reported up to 1916. The tumor produces nodular bulging of the appendix, but many tumors cannot be detected except by section of the entire appendix. The tumor varies from a microscopic lesion to a growth 2 cm. in diameter. The serosa is smooth and shiny over the nodule. When the nodule reaches sufficient size it projects into the lumen, producing partial or complete obliteration. On section, the carcinoid tumor may be yellowish gray, but it is frequently grayish white. It usually forms a small, hard, single, submucosal nodule. On section, it is found to be covered by the mucosa. MacCarty and McGrath found in 28 cases that the nodules were palpable on the exterior only in 5; the other 23 were discovered on gross section, carried out as a routine.

The microscopic examination of a carcinoid tumor of the appendix usually shows a small, compact, submucosal nodule. It seldom infiltrates the muscularis, but may erode the mucosa. The main portion of the mass consists of cords, sheets or irregularly arranged atypical epithelial cells. The cells are round, oval or polyhedral. In the peripheral portions of the larger masses, they assume a cubical appearance. The cells are definitely smaller than the columnar cells of the appendix and have no resemblance to the mucous cells. The cytoplasm is sparse and somewhat pale. It is frequently homogeneous, but vacuoles and fat globules may occur. The nucleus is prominent. It is round or oval and takes a deep basal stain on account of an abundant content of chromatin. Chromatin granules, as well as a fine network of chromatin threads, may occasionally be distinguished.

The cells are sometimes grouped about a space in such a manner as to suggest a vesicular or alveolar arrangement. The contents of spaces are stained a pale red by eosin. The stroma may vary from a few loose connective tissue fibers to an abundant deposition of coarse, collagenous or hyaline sheets of connective tissue. Bundles of muscle cells are often a portion of the stroma. When the colums of cells invade

the muscular layers, they may be isolated among bundles of smooth muscle. Lymphocytes may be found about the masses of carcinoid cells, but they are usually absent. The epithelial cells contain cytoplasmic granules which reduce an ammoniacal solution of silver. When fixed in solutions of chrome salts, the granules take a yellow color. In some carcinoid tumors of the appendix, anisotropic cytoplasmic granules or spherules have been described. The presence of silver or of argentaffine granules is considered a specific histochemical test for the identification of the carcinoid cell. Sprafke, however, recently showed that two carcinoid tumors examined by him did not contain any argentaffine cells.

The histogenesis of carcinoid tumors of the appendix is believed to be identical with carcinoid tumors of the small intestine. All important conceptions have been previously considered and need not be reconsidered.

The clinical course depends somewhat on the situation and size of the tumor. It may produce symptoms similar to those usually interpreted as chronic or mild recurrent appendicitis. Carcinoid tumors of the appendix which metastasized to the regional lymph nodes have been described by Hasegawa and Oberndorfer.[50] General metastasis has not been produced by a carcinoid tumor of the appendix.

A histologic study was made of 5 cases of carcinoid tumor of the appendix. The structure of these tumors indicates that morphologically they are closely similar to, if not identical with, carcinoid tumors of the small intestine. However, in the case of carcinoid tumors of the appendix, distant metastasis has not been described, and metastasis in the lymph nodes is extremely rare.

COMMENT

Only 9 cases of carcinoid tumors of the small intestine had been observed when Oberndorfer,[62] in 1907, presented his observations on 7 cases. On the morphologic and clinical evidence in this group of entirely benign tumors, he defined carcinoid tumors of the small intestine as small, usually multiple, submucosal, hard, grayish-white nodules usually situated in the ileum. The definition was appropriate at the time on the basis of the material observed, but the conception that carcinoid tumors of the small intestine are benign has remained, and is a general belief even at present. It seems to me that the definition of carcinoid tumors must express the significant fact that they may grow to a large size and produce intestinal obstruction, and that metastasis has occurred in more than 20 per cent of all cases reported.

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62. Oberndorfer, Siegfried: Karzinoide Tumoren des Dünndarms, Frankfurt. Ztschr. f. Path. **1**:426, 1907.

Few tumors have been given so many different names to designate their structure, clinical course and origin. Many investigators have been anxious to use a term that would express a specific derivation. Since 1910, the term carcinoid tumor of the small intestine has been used almost universally. Recent workers in this field still use the term carcinoid tumors even while simultaneously suggesting a new name.

Carcinoid tumors of the small intestine are not common. Only 2 cases in which the tumor was considered malignant have been observed in 12,000 necropsies performed in the department of pathology of the University of Minnesota. However, more than 104 cases have been reported in the literature. In about 20 per cent of all reported cases, metastasis has occurred. It may be that more cases have been observed, but only those reports were published which appeared to be of clinical interest. Many cases have been reported from a small number of German laboratories: Oberndorfer,[50] 20 cases, Toenniessen, 11 cases, Burckhardt,[31] 7 cases, and Hageman, 10 cases. This may be interpreted in two ways, either that the tumor does not occur at other places with the same frequency, or that it is not looked for at necrosy. The knowledge of this tumor has been based principally on the observation of single cases. So far as I know, my summary includes all authentic cases in the available literature. The summary begins with the first case published by Langhans in 1867, and includes the cases reported up to October, 1929. More than 104 cases of carcinoid tumors of the small intestine have been reported. Although certainly not common, it should be considered as a possible cause in obstruction of the small intestine, especially if the obstruction can be localized in the distal portion of the ileum.

A carcinoid tumor is usually considered to be small. In the 21 malignant lesions, the smallest lesion was 5 mm. and the largest 4.5 cm. in diameter, whereas in 83 benign lesions, the smallest lesion measured 1 mm. and the largest 2.5 cm. in diameter. The average size is from 5 mm. to 1 cm. in diameter. It is well to remember that by a consideration of size alone, it is impossible to differentiate this tumor from adenocarcinoma.

Since Lubarsch described his 2 cases of carcinoid tumors of the small intestine, the conception that the tumor is multiple has become firmly fixed as a general conception. But in the entire group of 104 cases, the tumor was multiple in only 35 cases and single in 60 of 95 cases in which this information was available. In the group of 21 cases in which the tumor was malignant, it was multiple in 8 cases and single in 11 cases; in the group of 60 cases in which the tumor was benign, the tumors were multiple in 27 cases and single in 49 cases. There was no definite relation of the number of nodules, the site, the age of the patient or the incidence of metastasis.

A determination of the most common site of the primary lesion of the carcinoid tumors in the small intestine is of importance to the pathologist and clinician. In 92 cases, the primary lesion was found in the duodenum in 2, in the jejunum in 11 and in the ileum in 79. The apparent predilection of this tumor for the ileum becomes more pronounced if one takes into consideration only the group in which the malignant changes were present. Twenty-one malignant lesions occurred in the ileum, and of these, 17 were in the distal third. In the group of 71 benign lesions, 58 were in the ileum, and 44 of these were in the distal third. In 2 cases the lesion was at the tip of a Meckel's diverticulum.

Although the primary lesion in the majority of reported cases has been nodular, in 5 of 84 cases it was annular. Four of the 5 annular lesions were found in the group of 21 malignant lesions.

None of the numerous suggestions advanced to explain the histogenesis of carcinoid tumors of the small intestine has received unanimous confirmation. The problem has been approached from many angles and by a number of ingenious methods. Parat,[63] Masson,[23] Dietrich, Kull [25] and others have made detailed embryologic studies in this field. Their conclusions do not agree. Parat and Masson [23] traced the type cell to the endoderm, Dietrich to the ectoderm and Kull to the mesoderm. Further information appears to be essential for the clarification of these contradictory conclusions.

The morphologic studies can be considered in two periods: before the application of stains which showed the intracellular granules and after the application of specific granular stains. During the first period the principal epithelial cells of the crypts of Lieberkühn or embryologic anomalies were considered as the source of carcinoid tumors of the small intestine. It is evident that the peculiar morphology and staining qualities of the cells were appreciated and by these qualities definitely distinguished from adenocarcinoma by Lubarsch in 1888. Bunting, in 1904, made a distinct contribution when he emphasized the resemblance of the cells to those which form basal cell carcinoma of the skin.

There are few supporters of the numerous hypotheses of the origin of carcinoid tumors from embryologic malformations, displacements or arrested development. The suggegstion by Huebschmann that carcinoid tumors originate from the chromaffin cells of Kultschitzky directed attention to a new approach to the investigation of this neoplasm. Credit should also be given to Oberndorfer,[29] who, in 1907, reported 7 cases of carcinoid tumor of the small intestines and observed that the tumor

63. Parat, M.: Contribution à l'histophysiologie des organes digestifs de l'embryon, Compt. rend. Soc. de biol. **90**:1023 (April 18) 1924.

takes a yellow stain when fixed in a solution of chromic acid and formaldehyde. Huebschmann, on the other hand, had not observed a case, and did not apply his idea. Numerous workers since 1914 have applied special stains to demonstrate the acid granules, chromaffin granules or argentaffine granules in the cytoplasm of the cells which form carcinoid tumors. The present conception of the basal granule cell is that reached by Kull, in 1925, who expressed the belief that the granules in the basal granule cell may take a chromaffin, acid or silver stain. In other words, this is a single cell type. The granules may, however, take various stains when in different functional stages. The detailed work of Masson [35] and Danisch must be carefully investigated and confirmed on a larger scale. No explanation of the histogenesis of carcinoid tumors of the small intestine presented up to the present time can be accepted without reservation.

The clinical significance of carcinoid tumors has not been correctly estimated or understood. The condition has not been diagnosed before operation or necropsy. This may be due to the false conception of this tumor as always small, uncommon and benign. Another factor is the absence of a summary of the reported cases. In an analysis of the data, it seems advisable to consider separately the group of 21 cases of malignant tumor and the 83 cases of benign tumor. In the group of 21 cases, there were definite evidences of intestinal obstruction in 10. The symptoms were nausea, vomiting, constipation with or without intermittent diarrhea, abdominal pain, loss of weight, cachexia, palpable abdominal tumor and enlargement of the liver. In one case the main complaint was cachexia and in another severe anemia. The chief clinical picture is that associated with obstruction of the small intestine, and it is found in about 50 per cent of the malignant cases. In the group of 83 benign cases, clinical evidences of a lesion were present in only 6. The symptoms and signs in 4 cases were similar to those in the malignant group which produced obstruction of the intestinal lumen. In 2 cases the symptoms and signs were suggestive of appendicitis.

There is cytologic similarity between carcinoid tumors of the small intestine and carcinoid tumor of the appendix. This morphologic resemblance has been considered sufficient basis for considering the 2 groups not only similar but identical. Bunting, Burckhardt,[31] and Krompecher expressed the belief that carcinoid tumors are basal cell carcinomas of the gastro-intestinal tract. Krompecher, in a study of this question, not only reached this conclusion, but subdivided carcinoid tumors into three groups dependent on the arrangement of the cells.

Similarities and differences in the clinical course of adenocarcinoma of the small intestine, basal cell carcinoma of the skin, carcinoid tumors

of the small intestine and carcinoid tumors of the appendix may be considered briefly. The malignant nature and metastatic tendencies of adenocarcinoma have recently been emphasized by Hellström.[64] He analyzed 70 cases from the literature and added 3 of his own in which resection had been performed for intestinal obstruction. The usual features of this neoplasm are too well known to be considered. Intestinal obstruction is usually the predominant symptom. Metastasis occurs early. In basal cell carcinoma of the skin, the opposite condition holds true. The age of the patient is usually more than 50 years, and the duration of the lesion from one to several years. The primary lesion is nearly always single, most lesions occur on the exposed portion of the skin, and metastasis is exceedingly rare. Only a few cases have been reported in which the tumor involved the regional lymph nodes. General metastasis has not been observed in any case. Carcinoid tumors of the appendix discovered in surgically removed specimens usually occur in persons less than 35 years of age. The symptoms produced are those of what is commonly called chronic appendicitis. In all proved cases of carcinoid tumor of the appendix, metastasis has not progressed beyond the regional lymph nodes. When a tumor of the small intestine is observed on roentgenoscopic examination or is found on exploratory laparotomy, it is essential to consider the possibility of a carcinoid tumor. It is not possible to make a differential diagnosis from an adenocarcinoma by physical signs or symptoms. A multiple tumor in the ileum strongly suggests a carcinoid tumor. All tumors of the small intestine, regardless of number, size, shape or distribution, should be examined microscopically for a correct pathologic diagnosis. The surgical procedure, and certainly the prognosis, will be influenced by the correct histologic interpretation.

The prognosis after removal of carcinoid tumors of the small intestine is favorable in the absence of metastasis. The fact must be recognized that metastasis occurred in 21 of 104 reported cases. In 38 per cent of 21 cases, general metastasis was present.

The only treatment for carcinoid tumors is surgical removal. This is essential when the primary tumor has reached more than 1 cm. in diameter. The primary tumor in all cases in which it was malignant was about this size or larger. If obstruction is produced, removal becomes imperative. The favorable prognosis after surgical removal in the cases reported by Decker, Bakke, and Primrose should be noted.

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64. Hellström, John: Primary Carcinoma in Jejunum and Ileum, Acta chir. Scandinav. **62**:465, 1927.

SUMMARY

Eleven additional cases of carcinoid tumor of the small intestine are reported, 3 of which were malignant and 8 of which were benign. Intestinal obstruction was caused by 3 of the malignant and 1 of the benign tumors. Five cases occurred in the seventh decade. The primary lesion was a single circumscribed nodule in 7 cases, multiple nodules in 3 cases and an annular constriction in 1 case. The primary lesion was in the jejunum in 2 cases and in the ileum in 9 cases. The size of the lesions varied from 0.2 cm. to 2 cm. in diameter.

In the available literature, there are reports of 21 malignant and 83 benign carcinoid tumors of the small intestine. The liver was involved in 8 cases, the regional lymph nodes in 11 cases and the serosa of the intestine in 3 cases. In 10 of 21 cases of malignant tumor and in 6 of 83 cases of benign tumor, the tumor produced intestinal obstruction. The primary lesion may be in the duodenum, jejunum or Meckel's diverticulum, but is most commonly situated in the distal portion of the ileum. The lesion is often multiple, but usually it is single. The largest number occurs in the fifth and sixth decades. There is no special predominance in either sex.

The histologic picture of carcinoid tumors of the small intestine suggests benign tumor, but metastasis occurs in about 20 per cent of the reported cases.

EXPERIMENTAL SHOCK *

VI. THE PROBABLE CAUSE FOR THE REDUCTION IN THE BLOOD PRESSURE FOLLOWING MILD TRAUMA TO AN EXTREMITY †

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In a recent communication,[1] the results of experiments in which the blood pressure was reduced to a low level in short periods of time were reported. The time which elapsed in these experiments between the initiation of the trauma and the reduction of the pressure to the desired level varied approximately from one to six hours. The difference in weight of the traumatized and nontraumatized extremites in all instances amounted to more than 4 per cent of the body weight. Johnson and Blalock [2] found that when a normal dog is bled 0.5 per cent of its body weight at one hour intervals, the blood pressure is usually reduced to a very low level after from eight to ten hours. No evidence was found for the action of a histamine-like substance which causes an immediate general loss of fluid from the blood stream. However, these experiments were probably not of sufficient duration to take into account the effects of decomposition products which are slow in their action.

The present experiments were undertaken in order to attempt to determine whether or not slowly acting decomposition products are responsible for the decline in pressure after injury to large masses of

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* In order to coordinate the previous reports with our major problem, this general title has been adopted. The previous communications, (a) Mechanism and Treatment of Experimental Shock: I. Shock Following Hemorrhage, Arch. Surg. **15**:762 (Nov.) 1927; (b) Trauma to Central Nervous System: Its Effect on the Cardiac Output and Blood Pressure: An Experimental Study, ibid. **19**:725 (Oct.) 1929; (c) Distribution of the Blood in Shock: The Oxygen Content of the Venous Blood from Different Localities in Shock Produced by Hemorrhage, by Histamine and by Trauma, ibid. **20**:26 (Jan.) 1930; (d) Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury in Dogs, ibid. **20**:959 (June) 1930, and (e) Trauma to the Intestines: The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure, ibid. **22**:314 (Feb.) 1931, are to be considered as papers I, II, III, IV and V of this series.

† Submitted for publication, April 16, 1930.

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1. Blalock, Alfred: Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury in Dogs, Arch. Surg. **20**:959 (June) 1930.

2. Johnson, G. S., and Blalock, A.: Unpublished Observations upon the Effects of the Loss of Whole Blood, of Blood Plasma and of Red Blood Cells.

muscle. The trauma was milder in degree, and the time that elapsed between the injury and the reduction of the pressure was longer than in the experiments that have been reported previously.

METHOD

Dogs were used in all experiments. Sodium barbital, 0.3 Gm. per kilogram of body weight administered intravenously, was employed as the anesthetic. The anesthesia which was produced by this amount of barbital was sufficiently profound to permit of no evidence of pain when the trauma was instituted. An occasional animal gave evidence of the regaining of consciousness during the latter part of the long period of observation. In each instance, the original anesthesia was supplemented by morphine. The employment of sodium barbital in many other experiments, in the amount used in these experiments, has shown that it usually does not alter the blood pressure. However, in an occasional experiment, barbital alone causes a progressive decline in the blood pressure.

The level of the mean blood pressure was used as the criterion of the degree of shock. The pressure was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. Infrequent observations on the pulse rate and the temperature were made.

In all experiments the injury was produced by striking one of the posterior extremities with a hammer. Most of the blows were struck over the thick flexor muscles of the thigh. The skin was not torn and no bones were broken. The length of time during which the leg was struck with the hammer was approximately ten minutes in most of the experiments. The trauma was always produced by the same person and the length of time that it would take a given amount of trauma to produce a decline in pressure could be estimated with fair accuracy in most instances.

After the blood pressure had reached the level which was desired, the differences in weight of the posterior extremities were determined. The level at which the amputations were performed was in the midabdominal region. After making a midline abdominal incision extending from the xyphoid process to the symphysis pubis, the aorta and vena cava were divided between ligatures. The symphysis pubis, was divided with a saw, and the bladder and the rectum were removed. The iliac vessels on each side were occluded. The upper and lower parts of the body were then severed by making transverse incisions in the midabdominal region at the same levels on both sides. Transverse division of the spinal column with a saw completed the amputation. In some experiments the lower part of the body was then divided into two equal halves by sawing longitudinally through the spinal column. The tail of the animal was then removed. In other experiments, division was effected by sawing just lateral to the vertebral column on each side. There was little loss of blood during these procedures.

This method of high amputation was chosen because it was found that trauma to an extremity produces an extravasation of blood not only into the local area but also into the loose tissues of the groin and flank. Amputation across the upper part of the thighs, the method used by Cannon and Bayliss,[3] does not take into account this fluid which has been lost at a higher level.

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3. Cannon and Bayliss: Note on Muscle Injury in Relation to Shock: Report of Shock Committee, Medical Research Committee, no. 26, 1919, p. 19.

In most instances, a sample of blood was obtained for a hemoglobin determination at the beginning of the experiment and also just before its termination. After the posterior extremities had been removed, an attempt was made to collect all of the fluid from them. Each of the extremities was placed in a large basin. Multiple incisions were made through each, and every part was washed thoroughly with physiologic solution of sodium chloride. The percentage of hemoglobin in the fluid in the two basins was then determined. These figures, when divided by the percentage of hemoglobin of the blood and multiplied by the amount of fluid in the basins, gave the amount of blood that was recovered from the two parts. Obviously, it is impossible by this method to collect all of the blood.

In additional experiments, the effects of injecting all of the fluid that could be obtained from traumatized and nontraumatized extremities into other dogs were studied. In both types of experiments, the amputation was performed in the midabdominal region. The rectum, the genito-urinary organs and the spinal column were removed. In the experiments on nontraumatized parts, both extremities were used since the amount of fluid that could be recovered was small as compared with that from extremities that had been traumatized. After the extremities had been placed in basins, multiple incisions were made into each, and all of the fluid that was obtainable was washed out with salt solution. The tissues were squeezed vigorously in the attempt to secure all of the fluid. In the experiments on traumatized extremities the injury was graded so that the time that elapsed between the initiation of the trauma and the reduction of the pressure to the desired level varied from three hours to three days. After the traumatized extremity had been removed, the fluid was obtained from it as in the case of the nontraumatized extremities. In both types of experiments, the fluid which was kept at body temperature was introduced into the external jugular vein of another dog anesthetized by barbital. The blood pressure of the recipient was recorded during the introduction of the fluid. The fluid was given rapidly in all experiments except one, the total time consumed in most experiments being approximately five minutes. The total amount of fluid obtained from the extremities plus the salt solution used in recovering it equalled in most experiments approximately 400 cc. In one experiment the fluid was injected into the muscles of the posterior extremities of a normal dog, and in another it was introduced into the peritoneal cavity.

RESULTS

The effects of mild leg trauma on the blood pressure and the difference in weight of the two extremities were determined in fifteen experiments. In five of these the blood pressure was higher than 70 mm. of mercury at the time of the amputation. These experiments are grouped together. In the remaining ten experiments, the blood pressure was lower than 70 mm. of mercury.

1. *Experiments in Which the Blood Pressure Was Higher Than 70 mm. of Mercury at the Time of the Amputation.*—The average length of time between the traumatization and the amputation of the extremities was forty-four hours and thirteen minutes. The average mean blood pressure just prior to the amputation in the five experiments was 108 mm. of mercury. The traumatized extremity was

definitely larger than the opposite normal one in all experiments. The average difference in weight of the two extremities amounted to 2.41 per cent of the body weight, the variation in the different experiments being from 1.62 to 3 per cent of the body weight. The amount of whole blood that was recovered from the traumatized extremities varied from 50 to 133 cc. There was an increase in the hemoglobin content of the blood in all experiments.

The observations in these experiments are given in table 1.

2. *Experiments in Which the Mean Blood Pressure Was Less Than 70 mm. of Mercury at the Time of Amputation.*—In five of these experiments, the animals were allowed to die, and in the remaining

TABLE 1.—*Experiments in Which the Mean Blood Pressure Remained at a Level Higher Than 70 Mm. of Mercury After Mild Leg Trauma*

Experiment	Weight of Dog, Kg.	Hemoglobin per Cent, Control	Hemoglobin per Cent, Before Amputation	Mean Blood Pressure, Mm. Hg, Control	Mean Blood Pressure, Mm. Hg Before Amputation	Time Interval Between Trauma and Amputation, Hr., Min.	Weight of Traumatized Leg, Gm.	Weight of Nontraumatized Leg, Gm.	Difference in Weight of Legs, Gm.	Per Cent of Body Weight	Blood from Traumatized Leg, Cc.	Blood from Nontraumatized Leg, Cc.
1	9.1	66	76	134	108	49:15	1,240	990	250	2.75	50	4
2	10.5	81	91	148	93	70:50	1,280	1,110	170	1.62	54	4
3	12.7	74	82	150	74	23	2,060	1,680	380	3.00	133	16
4	13.8	69	95	155	95	30	2,240	1,840	400	2.90	102	7
5	9.7	70	82	156	168	48	1,200	1,025	175	1.80		

five the mean blood pressure just prior to the amputation ranged from 64 to 69 mm. of mercury. The time interval elapsing between the traumatization and the termination of the experiment ranged from nineteen hours to forty-nine hours and forty-five minutes, the average duration being thirty-two hours and sixteen minutes. The average difference in weight of the two extremities in the ten experiments amounted to 3.66 per cent of the body weight, the individual figures for the different experiments varying from 2.48 to 5.53 per cent. In eight of the ten experiments the difference amounted to more than 3 per cent of the body weight. The quantity of whole blood recovered from the traumatized extremity varied from 40 to 154 cc. There was a concentration of the blood in all experiments in which hemoglobin determinations were performed.

The values for these experiments are given in table 2.

The posterior extremities of an animal that died thirty-nine hours after the right leg was traumatized. The difference in weight of the two extremities amounted to 4.81 per cent of the body weight. This is experiment 4 recorded in table 2.

TABLE 2.—*Experiments in Which the Mean Blood Pressure Was Reduced to Less Than 70 Mm. of Mercury by Mild Leg Trauma*

Experiment	Weight of Dog, Kg.	Hemoglobin per Cent, Control	Hemoglobin per Cent, Before Amputation	Mean Blood Pressure, Mm. Hg, Control	Mean Blood Pressure, Mm. Hg Before Amputation	Time Interval Between Trauma and Amputation, Hr., Min.	Weight of Traumatized Leg, Gm.	Weight of Nontraumatized Leg, Gm.	Difference in Weight of Legs, Gm.	Per Cent of Body Weight	Blood from Traumatized Leg, Cc.	Blood from Nontraumatized Leg, Cc.
1	11.5	85	107	162	64	49:45	1,840	1,505	335	2.91	105	8
2	11.2	..	..	134	66	26	1,700	1,310	390	3.48		
3	14.5	..	..	130	69	30:30	1,960	1,500	460	3.17		
4	16.0	78	92	153	Dead	39	2,470	1,700	770	4.81	154	13
5	20.5	87	..	174	Dead	30	2,940	2,240	700	3.41		
6	11.7	66	..	125	Dead	42	1,630	1,340	290	2.48		
7	6.1	69	100	134	66	17:30	970	765	205	3.36	40	4
8	9.3	58	69	122	66	29	1,425	910	515	5.53	114	10
9	13.4	70	..	158	Dead	40	2,190	1,640	550	4.10		
10	8.5	73	..	164	Dead	19	1,280	995	285	3.35		

The accompanying illustration shows the posterior extremities of an animal thirty-nine hours after one of the extremities was traumatized.

3. *The Effects of Introducing into Dogs the Fluid Obtained from the Nontraumatized Extremities of Other Dogs.*—Five experiments of this type were performed. In most instances, the dog that was traumatized was larger than the recipient of the fluid. In four of the five experiments there was a marked decline in the blood pressure either during or immediately after the introduction of the fluid. One of the dogs died five hours after the fluid was given. It is believed that the other four would have recovered had they been given the opportunity.

These five experiments are described briefly in the first part of table 3.

4. *The Effects of Introducing into Dogs the Fluid Obtained from the Traumatized Extremities of Other Dogs.*—Eleven experiments of this type were performed. In eight of these, the fluid was introduced rapidly into the external jugular vein, in one it was slowly given intravenously, in one it was injected into the muscles of the legs and in the remaining experiment it was introduced into the peritoneal cavity. The results in these experiments were extremely variable. The animal that received fluid into the muscles of the thigh died eight hours later, while the one that had fluid and lacerated muscle introduced into the peritoneal cavity recovered. In the one experiment in which the fluid was slowly introduced intravenously, the animal died two and one-half hours after the beginning of the injection and before it had been completed. In three experiments in which the fluid was rapidly introduced intravenously there was an initial rise in the blood pressure, while in the remaining five there was a marked decline. Seven of the eight animals died after the fluid was administered. The interval of time that elapsed between the introduction of the fluid and death varied from several minutes to twenty-four hours. In several instances, autopsy revealed blood-stained fluid in the peritoneal cavity, macroscopic hemorrhages in several organs and a thickened, grayish gallbladder. In three of four experiments in which an extremity of a very fat dog was traumatized, it was observed that the giving of the fluid from this extremity to another dog produced almost immediate death. The respirations stopped several minutes before the heart stopped beating. Short intervals of time separating the trauma to the extremity and the introduction of the fluid into another animal seemed to be associated with just as severe a reaction as did the longer intervals.

The results of these experiments are given in brief in table 3.

TABLE 3.—*The Effects of Introducing into Dogs the Fluid Obtained from Traumatized and Nontraumatized Extremities*

Experiment	Nature of Experiment	Time Interval Between Trauma and Amputation	Initial Effect of Injection on Blood Pressure	More Remote Effect of Injection on Blood Pressure	Comment
1	Normal extremities	No trauma	Fell from 130 to 58 mm. immediately after injection ended	Returned to normal control level four hours later	Animal recovered
2	Normal extremities	No trauma	Fell from 113 to 57 mm. during injection	Returned to normal control level three hours later	Later injection of equal amount of normal salt solution produced no alteration in blood pressure
3	Normal extremities	No trauma	Fell from 156 to 46 mm. during injection	Rose slightly one hour later; animal died 5 hours after injection	Autopsy showed bloody fluid in peritoneal cavity; edema of gallbladder; injection of duodenum; hemorrhages of liver and spleen
4	Normal extremities	No trauma	Slight rise in blood pressure during injection	Blood pressure remained at normal level	
5	Normal extremities	No trauma	Fell from 150 to 50 mm. during injection; returned to normal immediately	Practically normal 24 hours later	
6	Leg trauma	4 hours, 45 minutes	Rose from 100 to 145 mm.	Slow decline; death six hours later	Bloody fluid in peritoneal cavity; hemorrhages in various organs
7	Leg trauma	3 hours	Slow introduction of fluid; first rise, later fall	Slow decline; death 2½ hours after injection started	Bloody fluid in peritoneal cavity; hemorrhages in various organs
8	Leg trauma	17 hours, 30 minutes	Fell from 134 to 64 mm. and then rose to 150	Two hours later was 84; 4 hours later was 150	Animal killed 24 hours later; no free fluid; no gross hemorrhages; gallbladder normal; donor very fat
9	Leg trauma	50 hours	Fell from 120 to 77 mm. during injection; immediate rise to 130	Five hours later was 66; died 22 hours after injection	Temp. 92.8 F. before death; small amount of free fluid in peritoneal and pleural cavities; gallbladder thick-walled
10	Leg trauma	29 hours	Rose from 127 to 136 during injection	Slow decline; died 5 hours later	Blood-stained fluid in peritoneal cavity
11	Leg trauma	70 hours, 50 minutes	Immediate fall from 128 to 47 mm.	Died 8 minutes after injection was started	Donor very fat dog; breathing ceased several minutes before heart stopped beating; gallbladder presented normal appearance at autopsy
12	Leg trauma	23 hours	Immediate fall from 155 to 50 mm.	Died 7 minutes after injection was started	Donor very fat dog; gallbladder thick-walled and whitish; no free peritoneal fluid; respiratory death
13	Leg trauma	3 hours	Immediate fall from 118 to 20 mm.	Died 10 minutes after injection was started	Donor very fat dog; respiratory death
14	Leg trauma	26 hours	Rose slightly during injection	Slow decline; died 7 hours after introduction of fluid	No autopsy
15	Leg trauma	5 hours	No alteration in pressure	Died 8 hours later	Fluid was injected into thigh muscles; none intravenously
16	Leg trauma	5 hours	Not determined	Animal recovered	Fluid and lacerated muscle introduced into the peritoneal cavity

COMMENT

In the previous experiments [1] on trauma to large masses of muscle, the time that elapsed between the initiation of the trauma and the reduction of the pressure to a low level varied from one to six hours. Although the experiments of Cannon and Bayliss [3] are not described in detail, approximately the same interval of time elapsed. They found that there was not sufficient bleeding into the injured area to account by itself for the reduction in the blood pressure. Section of the upper lumbar cord in some of their experiments showed that the fall in blood pressure was not due to any general effect of the trauma on the circulation brought about by nervous agencies. It was believed that the continued fall in pressure following trauma was produced by the absorption of some depressant substance. In my experiments on severe trauma of short duration, the difference in the weight of the extremities in all instances amounted to more than 4 per cent of that of the total weight of the animal. Since bleeding a dog 4 per cent of its body weight during a similar period of time causes a marked decline in the blood pressure, the loss of blood into the injured area was believed to be responsible for the drop in the pressure. It was pointed out that the discrepancy between these results and those obtained by Cannon and Bayliss was probably due to the difference in the methods by which the posterior extremities were amputated. However, probably neither of these groups of experiments was of sufficient duration to rule out the effects of metabolites which are very slow in their actions. The time which elapsed between the traumatization and the amputation of the extremity in the present experiments varied from nineteen to seventy hours. Experiments of such long duration have the disadvantage that the animals have to be deeply anesthetized during the entire period and this probably alters somewhat their ability to tolerate such procedures as loss of blood. Deprivation of water and food alone for several days results in concentration of the blood [4] and probably in a decrease in the ability to withstand hemorrhage. The giving of barbital does not alter appreciably the immediate tolerance to hemorrhage. The effect of barbital on the ability of the animal to withstand hemorrhage twenty-four or more hours after its administration has not been accurately determined, but it was definitely decreased in the several experiments which were performed. Dale [5] found that a cat that had been anesthetized by ether for two hours would tolerate only

4. Underhill, F. P., and Kapsinow, R.: The Influence of Water Introduction upon Blood Concentration Induced by Water Deprivation, J. Biol. Chem. **54**:459, 1922.

5. Dale, H. H.: Supplementary Note on Histamine Shock, Report of Shock Committee, Medical Research Committee, no. 26, 1919, p. 15.

one-fifth as much histamine without dying as would the same cat without an anesthetic. Similar studies have not been performed with histamine and barbital.

In the five experiments in which the blood pressure was higher than 70 mm. of mercury at the time of the amputation, the average difference in the weight of the two extremities was 2.41 per cent of the body weight. The blood pressure at the termination of four of these experiments was higher than 90 mm. of mercury. There was an easily apparent difference in the size of the extremities in all experiments. It is believed but not proved that the size of the traumatized extremity was smaller in some of these extremities at the time of the amputation than it was thirty-six hours after the receipt of the injury.

In the ten experiments in which the pressure was reduced to less than 70 mm. of mercury the average difference in the weight of the two extremities was 3.66 per cent of the body weight. In the experiments in which it was determined, the whole blood that was recovered accounted for only about one fourth of this difference. Obviously it was impossible, by the method used, to recover all of the blood. However, it can be stated with certainty that the red blood cells constituted a relatively small part of the fluid which escaped into the injured area. The proportion was much smaller than in the previously reported experiments in which the trauma was more severe. The greater part of the fluid which was lost was probably blood plasma. There was concentration of the blood in all experiments in which determinations of the hemoglobin were performed. These tests were performed on blood from the femoral vein of the nontraumatized extremity. They indicate the minimum loss of blood through filtration of the plasma as any local retention of red cells would decrease the percentage. Observations of previous investigators indicate that the fluid that was lost into the traumatized area was mainly the plasma of the blood. Starling[6] demonstrated that the walls of the blood vessels are normally impermeable to colloids. Scott[7] showed that there is no protein in the fluid absorbed from the tissue spaces by the blood, although the fluid in these spaces contains protein. Dale and Laidlaw[8] found that shock that is produced by histamine is not accompanied by an increase of the plasma proteins, and they expressed their belief that whole plasma rather than water escaped into the tissues through the altered capillaries.

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6. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, J. Physiol. **19**:312, 1896.

7. Scott, F. H.: The Mechanism of Fluid Absorption from Tissue Spaces, J. Physiol. **50**:157, 1915-1916.

8. Dale and Laidlaw: Histamine Shock, J. Physiol. **52**:355, 1918.

Gasser, Erlanger and Meek [9] produced shock by clamping the aorta, and effected filtration of the whole plasma. Underhill [10] and his associates stated that when fluid leaves the tissues and blood in response to local inflammatory reactions the fluid poured on the surface is plasma or at least modified plasma. In regard to pulmonary edema they stated, "Certain it is that in war gas poisoning in the production of pulmonary edema the fluid entering the lungs has almost the same composition as the blood plasma." The character of the fluid that escapes into tissues of the extremity that has been traumatized will be the study of a future investigation but it seems almost certain that its composition is practically that of whole blood plasma.

If it be granted for the moment that the fluid that is lost into the traumatized extremity has approximately the same composition as has whole blood plasma, the question then arises as to whether or not the loss of this amount of plasma could account for the reduction in the blood pressure that was found. Information in this respect is not definite. Kallius [11] stated that the serum and not the red blood cells is the important element in the replacement after an acute loss of blood. Abel, Rountree and Turner [12] found that it was possible to withdraw by repeated bleedings in a single day a volume of blood more than twice that contained in the body, with no apparent injury to the animal if only the corpuscles suspended in Locke's solution were returned after each bleeding. However, in the present experiments there was no replacement of the fluid which was lost. Almost certainly there is some passage of water from the tissues into the blood stream, but probably a considerable portion of this is lost in the urine and the expired air. Morawitz [13] found that he could keep animals alive after replacing two thirds of serum proteins by gum. Saline solution would not serve the purpose. Bayliss [14] produced concentration by removing a part of the blood, defibrinating and centrifuging it and reinjecting the corpuscular

9. Gasser, Erlanger and Meek: Studies in Secondary Traumatic Shock: IV. The Blood Volume Changes and the Effect of Gum Acacia on Their Development, Am. J. Physiol. **50**:31, 1919.

10. Underhill, F. P.; Carrington, G. L.; Kapsinow, R., and Pack, G. T.: Blood Concentration Changes in Extensive Superficial Burns and Their Significance for Systemic Treatment, Arch. Int. Med. **32**:31 (July) 1923.

11. Kallius, H. W.: Experimentell Untersuchungen über die Wirkung des Serums bei der vitalen Bluttransfusion, Deutsche Ztschr. f. Chir. **212**:289, 1928.

12. Abel, Rowntree and Turner: Plasma Removal with Return of Corpuscles (Plasmaphaeresis), J. Pharmacol. & Exper. Therap. **5**:625, 1913-1914.

13. Morawitz: Beitr. z. Chem. Phys. u. Path. **7**:153, 1906.

14. Bayliss, W. M.: The Action of Gum Acacia on the Circulation, J. Pharmacol. & Exper. Therap. **15**:29, 1920.

layer. The result of the experiment in which the largest proportion of plasma was removed is as follows:

When 47 per cent of the plasma had been removed, the blood pressure had fallen to 75 mm. of mercury from its original value of 163 mm. The animal died at the following removal of blood equal to about 20 per cent of its original blood volume. The method is therefore impracticable; but it makes evident the importance of the mere volume of the blood, since practically all the corpuscles were returned. Similar experiments in which the whole of the defibrinated blood was returned to circulation had no such fatal effects.

Gasser, Erlanger and Meek [9] determined the blood volume in a large series of dogs and found the average to be 9.7 per cent of the body weight. They estimated that the plasma constitutes 60 per cent of the volume of the blood. The average difference in weight of the two extremities in the present experiments in which the blood pressure was reduced to less than 70 mm. of mercury was 3.66 per cent of the body weight. If all the fluid that was lost was whole plasma, this would mean that only 37 per cent of the original plasma was left in the blood stream. This figure is definitely too low, as a moderate amount of the loss consisted of red blood cells. However, the loss was sufficient to cause a marked elevation in the viscosity of the blood, which resulted in a great increase in the internal friction of the red cells against the vessel walls as has been demonstrated by Trevan.[15] The walls of the capillaries in the traumatized area allow the escape of proteins. Concerning this condition, Bayliss [14] stated:

Since it is the osmotic pressure of the proteins that preserves the blood from a rapid filtering away of its liquid portion into the tissue spaces and causes re-absorption of fluid from them, while this osmotic pressure can only be effective as long as the concentration of proteins is unequal on the two sides of the membrane, it will be clear that if the proteins can diffuse through the membrane of the capillary wall, their concentration will become equal on both sides and there is no longer any force resisting filtration or causing re-absorption.

Since the difference in the weight of the two extremities in most of the present experiments represented such a large volume of fluid which was almost certainly largely whole plasma, it is believed that the increased permeability of the capillaries is limited mainly, if not solely, to the traumatized area and that the decline in blood pressure results from the decrease in blood volume due to the loss into the injured part.

The experiments in which the fluid was taken from a traumatized extremity and injected into another dog were undertaken with the idea that the effects of trauma of long duration might be different from those of short duration. It was thought that this might throw some light on the rôle played by the decomposition products in the production

15. Trevan: Biochem. J. **12**:60, 1918.

of the low blood pressure. The experiments were unsatisfactory for this purpose since it was found that the material that was obtained from normal extremites usually caused a decline in the blood pressure. In the experiments on traumatized extremities, the time interval elapsing between the trauma and removal varied from three to seventy hours, and no difference in the effects on introduction into other dogs was determined. Death resulted in most of the experiments. In three experiments in which the injured extremity was removed from a very fat dog, immediate death resulted in the recipient on the introduction of the fluid. The significance of this is not known.

SUMMARY

In experiments on dogs anesthetized by barbital the effects of mild trauma to one of the extremities were studied. The time interval that elapsed between the initiation of the trauma and the amputation of the extremities varied from seventeen to seventy hours. In five experiments the average of the mean blood pressures was 108 mm. of mercury at the time of the amputation, and the average difference in weight of the two extremities amounted to 2.41 per cent of the body weight. In ten experiments the mean blood pressure was less than 70 mm. of mercury at the time of the amputation and the difference in weight of the two extremities was 3.66 per cent of the body weight. Previous experimental work indicates that the fluid that was lost was mainly the whole plasma of the blood. Reasons are given for the belief that the loss of fluids into the traumatized region was the chief if not the sole cause for the reduction in the blood pressure.

In additional experiments the effects of injecting fluid obtained from extremities which had been traumatized into other dogs were studied. No conclusions could be drawn from these experiments, since the introduction of fluid obtained from nontraumatized extremities into other dogs finally caused a decline in the blood pressure.

EXPERIMENTAL SHOCK

VII. THE IMPORTANCE OF THE LOCAL LOSS OF FLUID IN THE PRODUCTION OF THE LOW BLOOD PRESSURE AFTER BURNS *

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The literature on the subject of burns is voluminous and the theories that have been offered as an explanation for the effects produced by burns are numerous. In 1898, the four prevailing theories as to the cause of death after extensive burns when Bardeen [1] reviewed the literature and presented his excellent studies were:

1. It is due to interference with the respiratory, the excretory and the heat regulating functions of the skin. 2. It is due to vasomotor exhaustion. 3. It is caused by injury to the red blood cells with resulting thrombosis. 4. It is due to toxemia. Advances in the understanding of the mechanism whereby extensive burns produce death have not been marked during the past thirty years. The prevailing theory is and was that the deleterious effects are due to the absorption of toxic products from the injured area. On the contrary, distinct advances have been made in the treatment for burns in recent years, and the mortality rate has been lowered considerably. This is due in part to the fact that the importance of keeping the wounds from becoming infected has been appreciated. The use of agencies which supposedly prevent the absorption of toxins, such as epinephrine (Douglas [2]) and tannic acid (Davidson [3]), has given encouraging results. Robertson [4] attributed the good results which he obtained by using the exsanguination-transfusion method to the elimination of the toxins.

* Submitted for publication, April 16, 1930.

* From the Department of Surgery, Vanderbilt University.

1. Bardeen, C. R.: A Review of the Pathology of Superficial Burns, with a Contribution to Our Knowledge of the Pathological Changes in the Organs in Cases of Rapidly Fatal Burns, Johns Hopkins Hosp. Rep. **7**:137, 1898.

2. Douglas, B.: Restriction of Rate of Flow and Interchange in Capillaries, J. A. M. A. **81**:1937 (Dec. 8) 1923.

3. Davidson, E. C.: Tannic Acid in the Treatment of Burns, Surg. Gynec. Obst. **41**:202, 1925.

4. Robertson, B.: Blood Transfusion in Severe Burns in Infants and Young Children, Canad. M. A. J. **11**:744, 1921.

Underhill and his associates [5] believed that the ill effects following burns were due to marked concentration of the blood, and they obtained excellent results by simply forcing fluids.

In previous experiments [6] the amount of fluid that was lost from the blood vessels in the injured area after trauma to an extremity and to the intestines was determined. The present experiments were undertaken in order to determine the amount of fluid that escapes from the blood vessels at the site of extensive burns.

METHOD

Dogs were used in all experiments. A sufficient amount of sodium barbital (0.3 Gm. per kilogram of body weight administered intravenously) was given to keep the animal deeply anesthetized during the experiment. The blood pressure was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. The level of the mean blood pressure was used as the criterion of the degree of shock. The hair was removed from the body and extremities of the animals by the use of either fine clippers or a razor. The longitudinal midlines on both the dorsal and ventral surfaces of the dogs were marked with ink. A sample of blood for a hemoglobin determintaion was obtained from the femoral vein. With the animals profoundly anesthetized, varying amounts of one half of the body surface were burned with soldering irons. No attempt was made to measure the surface area which was burned, but in the greater portion of the experiments it equalled approximately one third of the entire body surface. In several experiments the area was definitely less than that. The time during which the irons were applied intermittently varied approximately from ten to forty minutes. The blood pressure was determined at infrequent intervals throughout the experiments. After a decline in blood pressure of varying degree had been obtained in the different experiments, the amount of fluid that had accumulated in the burned area was determined. This was accomplished by dividing the animal's body into two equal halves. Incisions into the skin both dorsally and ventrally were made along the lines that had been marked at the beginning of the experiment. This was necessary, because the skin became retracted toward the burned side. The recti abdominales muscles were separated in the midline by an incision extending from the xiphoid process to the symphysis pubis. A saw was employed in splitting the sternum in the midline in a longitudinal direction. The animal's neck was cut across in a transverse direction at the same levels on the two sides. A saw was used for cutting across the cervical spinal column. The head of the animal was discarded. The symphysis pubis was divided with a saw. All of the intra-abdominal and intraperitoneal organs,

5. Underhill, F. P.; Carrington, G. L.; Kapsinow, R. K., and Pack, G. T.: Blood Concentration Changes in Extensive Superficial Burns and Their Significance for Systemic Treatment, Arch. Int. Med. **32**:31 (July) 1923.

6. Blalock, A.: Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury in Dogs, Arch. Surg. **20**:959 (June) 1930; Trauma of Intestines: The Importance of the Local Loss of Fluid in the Production of Low Blood Pressure, ibid. **22**:314 (Feb.) 1931; Experimental Shock: VI. The Probable Cause for the Reduction in the Blood Pressure Following Mild Trauma to an Extremity, this issue, p. 598.

including the diaphragm, were removed en masse. Turning to the dorsal surface of the animal, the skin incision was extended through the muscles on each side immediately lateral to the spinous processes. Employing a saw and beginning in the lower cervical region on each side, the ribs were divided at their junctions with the spinal column and the sacro-iliac joints were cut across. This resulted in a complete removal of the spinal column and tail which were discarded. The two halves of the body were then weighed and the difference in weight was determined. In eight of the experiments a sample of blood was obtained for a hemoglobin determination just prior to the performance of the amputation.

RESULTS

The application of heat to the skin of a dog does not cause blisters. There is no weeping from the surface of the skin. The appearance

The Effects of Burns

Experiment	Weight of Dog, Kg.	Time Interval Between Burn and Amputation, Hr., Min.	Hemoglobin, per Cent, Control	Hemoglobin, per Cent, Before Amputation	Blood Pressure, Mm. Hg, Control	Blood Pressure Before Amputation, Mm. Hg.	Weight of Burned Side, Gm.	Weight of Non-burned Side, Gm.	Difference in Weight of Sides, Gm.	Per Cent of Body Weight
1	10.34	17	85	117	118	Dead	1,945	1,630	315	3.05
2	11.5	15	75	...	117	Dead	3,590	3,260	330	2.87
3	12.2	21	..	...	110	Dead	3,820	3,350	470	3.85
4	10.1	11	..	...	122	50	3,170	2,850	320	3.17
5	11.4	10:30	..	...	125	80	3,455	3,130	325	2.85
6	12.7	17	77	130	143	Dead	4,245	3,890	355	2.80
7	13.29	14:30	65	...	125	Dead	4,085	3,850	235	1.77
8	14.7	12	63	109	98	30	4,760	3,880	880	5.98
9	13.2	26	62	...	123	36	3,870	3,490	380	2.92
10	11.25	24	60	86	120	28	3,470	3,100	370	3.29
11	9.9	16	76	...	155	Dead	2,920	2,700	220	2.22
12	7.4	6	50	78	160	66	2,180	1,800	380	5.14
13	10.1	6	78	109	150	80	3,410	3,180	230	2.28
14	15.2	10	..	...	150	Dead	4,860	4,160	700	4.61
15	12.5	6	76	94	150	66	3,970	3,590	380	3.04
16	9.4	24	70	98	143	82	1,650	1,420	230	2.34
17	18.6	11	68	...	165	Dead	2,820	2,220	600	3.23
18	6.6	15	..	...	130	Dead	2,050	1,740	310	4.70

produced is similar to that seen after the application of tannic acid to a burned area in the human being. The skin feels much like leather. After the elapse of varying periods of time following the burn, depending on its severity, the subcutaneous tissues feel thickened and edematous.

Eighteen experiments were performed. The interval of time that elapsed between the burning and the division of the animal varied in the different experiments from six to twenty-six hours, the average time in all experiments being fourteen hours and thirty-three minutes In three instances the mean blood pressure was 80 mm. of mercury or

more at the termination of the experiment, in six it varied from 28 to 66 mm. of mercury and the remaining nine animals were allowed to die. In all experiments, the average difference in weight of the two sides of the body expressed in percentage of the initial weight of the animals was 3.34. In fourteen of the eighteen experiments the difference amounted to more than 2.75 per cent of the body weight. The figures for all experiments are given in the accompanying table.

Incisions into the burned area revealed the cause for the increase in weight of that side. The subcutaneous tissues were markedly edematous. That all the fluid did not accumulate immediately after the area was burned was shown by making incisions at various times after the injury and noting the progressive formation.

In the eight experiments in which hemoglobin determinations were performed, the burns caused a marked concentration of the blood. If the percentage of hemoglobin at the beginning of the experiments is considered to be 100, the average percentage at the termination is found to be 148.

COMMENT

In previous communications [6] the amount of fluid that was lost from the injured area after severe trauma to an extremity, after mild trauma to an extremity and after trauma to the intestines was reported. Red blood cells constituted a small part of the loss after mild trauma to an extremity and after trauma to the intestines, while after severe trauma to an extremity the fluid that escaped was largely whole blood. It was concluded that the escape of fluid from the blood stream in the traumatized area was the chief if not the sole factor responsible for the reduction in the blood pressure. The fluid that escapes from the blood vessels into the subcutaneous tissues of a burned area contains practically no red blood cells. From the work of previous investigators, it would be expected that this fluid would have practically the same composition as the plasma of the blood. Gasser, Erlanger and Meek [7] found that the protein content of the blood plasma underwent no marked change during the process of the concentration of the blood after the aorta had been clamped, and they believed that the plasma was lost mainly as a whole. Underhill [5] stated that the fluid that escapes into the lungs in the pulmonary edema produced by war gases has almost the same composition as the blood plasma. Beard and I [8] in unpublished

7. Gasser, Erlanger and Meek: Studies in Secondary Traumatic Shock: IV. The Blood Volume Changes and the Effect of Gum Acacia on Their Development, Am. J. Physiol. **50**:31, 1919.

8. Beard and Blalock, A.: Unpublished Determinations on the Composition of the Fluid Which Escapes from the Blood Vessels in Leg Trauma, Intestinal Trauma and Burns, 1930.

observations found that the fluid that collects in the subcutaneous tissues after burns has almost as high a protein content as has the plasma of the blood.

The average difference in weight of the two sides of the body in the present experiments amounted to 3.34 per cent of that of the body. The question arises as to whether or not the loss of this amount of plasma could account for the reduction in the blood pressure. Even if it could be definitely proved that the decline in pressure in the present experiments was due solely to the loss of plasma, it would not rule out the action of possible toxic products after burns of longer duration. It is difficult to interpret the results of experiments of very long duration in which profound anesthesia and deprivation of food and water are complicating factors. In the present experiments the longest interval of time elapsing between the application of heat and the termination of the experiment was twenty-six hours. The incomplete experiments of Johnson and myself,[9] in which an amount of blood which equals 0.5 per cent of the body weight is removed at one hour intervals, show that it is usually necessary to remove at least 4 per cent before the mean blood pressure will remain below 70 mm. of mercury. As regards the removal of plasma and reinjection of the cells over a similar period of time, it is found that the blood pressure is usually reduced to a low level after plasma amounting to approximately 3.5 per cent of the body weight has been removed. Bayliss[10] found that the removal of 47 per cent of the plasma in a cat caused a reduction in the blood pressure from 163 to 75 mm. of mercury. The animal died following the removal of blood equal to about 20 per cent of its original blood volume. Gasser, Erlanger and Meek[7] determined the blood volume in a large series of dogs and found the average to be 9.7 per cent of the body weight, and they estimated that the plasma constitutes 60 per cent of the weight of the blood. On comparing the loss of plasma in the present experiments (approximately 3.34 per cent of the body weight) with the estimated total of the animal, it is found that approximately 57 per cent of the total plasma escaped from the circulating blood stream. It is apparent that the loss of such a large amount of plasma would cause a concentration of the blood and an increase in the friction between the red blood cells and the walls of the vessels. It is likely that some of the fluid that was lost from the blood stream was replaced by the passage of water from the tissues of the body. Since no fluids were administered during the experiment, probably

9. Johnson and Blalock, A.: Unpublished Observations upon the Comparative Effects of the Loss of Whole Blood and of Plasma, 1930.

10. Bayliss, W. M.: The Action of Gum Acacia on the Circulation, J. Pharmacol. & Exper. Therap. **15**:29, 1920.

a large proportion of this was lost in the urine and in the expired air. At any rate, the passage of water from the tissues to the blood stream would not result in a replacement of the protein of the plasma. In addition to the loss of fluids in the urine and the expired air, another source, probably of small importance, is the dehydration of the skin produced as a direct result of the local application of heat. All of these factors are neglected in the determinations of the loss of fluid from the blood stream.

Underhill,[11] from his studies on poisoning by war gases, concluded that concentration of the blood exceeding the normal by 25 per cent is attended by grave symptoms and that a level maintained at 40 per cent or more above the normal is usually followed by death. The average increase in the concentration of the blood in the present experiments was 48 per cent. Whether the concentration of the blood is due to the loss of fluid exclusively into the injured area or whether there is a general increase in capillary permeability with loss of fluid as a result of toxic products cannot be stated definitely from the present experiments. The experiments of Bayliss and of Johnson and myself indicate that it is due solely or almost to the loss of fluid into the burned area alone. Bardeen[1] found swelling and focal degenerations of the lymphatic tissues of the body after burns. Weiskotten[12] stated that the suprarenal glands were swollen and deep red. There is a great amount of other good evidence which indicates that a toxin which exerts a general effect is formed. However, it is impossible to escape the fact that the loss of such large amounts of whole plasma into the burned area must play an important part in causing a reduction in the blood pressure as a result of the diminution in the blood volume. Regardless of whether or not death is due solely to the loss of plasma, the present experiments indicate that the fluid loss probably is the initiating factor in the decline of blood pressure. After the blood volume is reduced and the blood is very concentrated, it is likely that toxins if present, even in small amounts, will exert deleterious effects since elimination by the kidneys is greatly reduced. In the human being, the factor of loss of fluid after burns may be even more important than in the dog, since there is frequently copious weeping from the injured skin in man, and this is not encountered in dogs. It is entirely possible that such agencies as tannic acid and epinephrine exert their beneficial effects by preventing loss of fluids rather than by stopping the absorption of toxins.

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11. Underhill, F. P.: The Lethal War Gases: Physiology and Experimental Treatment, New Haven, Conn., Yale University Press, 1920.

12. Weiskotten, H. G.: Histopathology of Superficial Burns, J. A. M. A. **72**:259 (Jan. 25) 1919.

SUMMARY

The effects of burns on the escape of fluid into the tissue spaces of the injured area have been determined in eighteen dogs anesthetized deeply by barbital. Varying amounts of one half of the body surface were burned, and the difference in weight of the two halves of the body was determined. In all instances the burned side was heavier, the average difference in weight in all experiments being 3.34 per cent of the total weight of the dog. The important rôle that this probably exerts in the reduction of the blood pressure has been discussed.

EXPERIMENTAL SHOCK

VIII. THE COMPOSITION OF THE FLUID THAT ESCAPES FROM THE BLOOD STREAM AFTER MILD TRAUMA TO AN EXTREMITY, AFTER TRAUMA TO THE INTESTINES AND AFTER BURNS *

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In previous communications [1] the amount of fluid that is lost from the blood stream at the site of injury after severe trauma to an extremity, after mild trauma to an extremity, after trauma to the intestines and after burns was reported. When an extremity is traumatized severely, the fluid that escapes into the injured subcutaneous tissues and muscles consists largely of whole blood. Some red blood cells escape from the blood vessels after mild trauma to an extremity and after trauma to the intestines, but the proportion is much smaller than after severe trauma. Burns are associated with the escape of clear fluid with few red cells into the subcutaneous tissues. Gasser, Erlanger and Meek [2] found that the protein content of the plasma of the blood underwent no marked change during the process of the concentration of the blood after clamping the aorta, and they believed that the loss was for the most part whole plasma. Underhill [3] stated that the fluid that escapes in the pulmonary edema produced by war gases has nearly the same composition as the blood plasma.

It would be expected that the loss of whole plasma would be followed by more deleterious effects than would result from the loss of diluted plasma or of water. The present experiments were undertaken

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* From the Department of Surgery of the Vanderbilt University.

1. Blalock, Alfred: Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury, Arch. Surg. **20**:759 (June) 1930; Trauma to the Intestines: The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure, ibid. **22**:314 (Feb.) 1931; Experimental Shock: VI. The Probable Cause for the Reduction in the Blood Pressure Following Mild Trauma to an Extremity, this issue, p. 598; Experimental Shock: VII. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, this issue, p. 610.

2. Gasser, Erlanger and Meek: Studies in Secondary Traumatic Shock: IV. The Blood Volume Changes and the Effect of Gum Acacia on Their Development, Am. J. Physiol. **50**:31, 1919.

3. Underhill, F. P.: The Lethal War Gases, Physiology and Experimental Treatment, New Haven, Conn., Yale University Press, 1920.

in order to determine the composition of the fluid that escapes into or from the injured area because of several different procedures.

METHODS

Dogs were used in all experiments. The animals were deeply anesthetized by sodium barbital (0.3 Gm. per kilogram of body weight given intravenously). The level of the mean blood pressure was used as the criterion of the degree of shock. This was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. In some instances, samples of blood were obtained from the femoral vein at the beginning and termination of the experiments, and the hemoglobin was determined with a Sahli hemoglobinometer.

Samples of blood and of fluid were collected at the same time if possible. In some experiments the blood and fluid were oxalated while in others the analyses were performed on the serum. The results were approximately the same whether plasma or serum was used.

The analyses of fluid and plasma or serum were carried out as follows. The sugar was determined by the method of Benedict.[4] The sodium sulphate, which was kept as the concentrated solution, was added with the other reagents at the time of the determination. The nonprotein nitrogen was determined by the method of Folin and Wu.[5] The chlorides were determined by the method of Whitehorn.[6] The Gunning[7] modification of the Kjeldahl method was used in determining the total nitrogen. One cubic centimeter of plasma or serum was the amount used in all experiments. The mixture was heated for more than three hours. The time of distillation was forty-five minutes. One-tenth normal sulphuric acid was used for the absorption of the ammonia, and the excess was titrated with one-tenth normal sodium hydroxide. The figures corresponding to the total nitrogen were multiplied by the factor 6.25 for obtaining the figures for total protein which are used in the tables.

RESULTS

1. *Mild Trauma to an Extremity.*—Four experiments were performed in which one of the extremities was struck repeated blows with a hammer. The skin was not torn, and no bones were broken. In three of the four experiments, samples of blood were obtained for the various analyses before the trauma was instituted. The time interval which elapsed between the initiation of the trauma and the reduction of the blood pressure to the desired level varied from twenty-two to thirty-one hours. The mean blood pressure at the time of the termination of the experiment in two instances was above 90 mm. of mercury and in two instances was below 50 mm. The trauma was followed by a definite concentration of the blood in all experiments. After the blood pressure had reached the desired level, approximately 15 cc. of blood was removed from the femoral vein. An incision was then made

4. Benedict, S. R.: The Estimation of Sugar in Blood and Normal Urine, J. Biol. Chem. **68**:759, 1926.

5. Folin and Wu: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919.

6. Whitehorn, J. C.: A System of Blood Analysis, J. Biol. Chem. **45**:449, 1920.

7. Gunning, J. W.: Ztschr. f. anal. Chem. **28**:188, 1889.

into the traumatized area and enough of the subcutaneous tissues to yield about 10 cc. of fluid was removed and centrifugated.

The chloride content of the blood plasma was approximately the same at the beginning and the end of the experiments. The fluid recovered from the traumatized area had approximately the same chloride content as the plasma of the blood. The sugar content of the blood plasma was lower at the end than at the beginning of the experiments. The sugar content of the blood plasma was higher than that of the fluid in all experiments. The abnormally high values for sugar content

TABLE 1.—*The Composition of the Fluid Obtained from the Subcutaneous Tissues After Mild Trauma to an Extremity*

Experiment	Time Between Trauma and Amputation, Hr.	Time Sample Was Obtained	Control Blood Pressure, Mm. Hg	Blood Pressure Before Amputation, Mm. Hg	Control Hemoglobin, per Cent	Hemoglobin Before Amputation, per Cent	Chlorides in Blood Plasma, Mg. per 100 Cc.	Chlorides in Fluid of Leg, Mg. per 100 Cc.	Sugar in Blood Plasma, Mg. per 100 Cc.	Sugar in Fluid of Leg, Mg. per 100 Cc.	Nonprotein Nitrogen in Blood Plasma, Mg. per 100 Cc.	Nonprotein Nitrogen in Fluid of Leg, Mg. per 100 Cc.	Total Protein in Blood Plasma, per Cent	Total Protein in Fluid of Leg, per Cent
1	30	Just before amputation	156	95	69	95	639 Serum	627	100 Serum	64	90 Serum	80	5.0	6.3
2	25	Control, before trauma	140	...	103	...	660	...	123	...	35	...	6.4	...
		Just before amputation	...	42	...	115	622	636	76	75	63	66	7.1	8.0
3	31	Control, before trauma	143	...	68	...	607	...	166	...	34.2	...	...	...
		Just before amputation	...	92	...	89	650	686	137	117	48	60	9.9	9.2
4	22	Control, before trauma	170	...	88	...	660	...	186	...	31	...	6.7	...
		Just before amputation	...	48	...	112	633	613	133	80	108	100	7.7	10.6

are probably due to the barbital anesthesia. The nonprotein nitrogen content was definitely higher at the end than at the beginning of the experiment. The values for the fluid from the traumatized extremity were approximately the same as those for the blood plasma. In the two experiments in which it was determined, the total protein of the plasma was greater at the termination than at the beginning of the experiments. In three of the four experiments, the total protein content of the fluid from the traumatized extremity was higher than that of the plasma.

The results of these four experiments of mild trauma to an extremity are given in table 1.

2. Trauma to the Intestines.—Five experiments were performed. Before the traumatization was begun, the blood pressure and the hemoglobin were determined and a sample of blood was obtained from the femoral vein for the various analyses. The trauma was produced by pinching the intestines between the fingers. The intestines were not delivered from the peritoneal cavity and the fluid that escaped from the traumatized areas accumulated in the peritoneal cavity. The intestines were pinched continuously in most of the experiments, and the time that elapsed between the initiation of the trauma and the reduction of the pressure to a level less than 70 mm. of mercury was approximately six hours. At intervals throughout the course of the experiments, the blood pressure was determined, a sample of blood was obtained from the femoral vein and fluid was collected from the peritoneal cavity. This

TABLE 2.—*The Composition of the Fluid that Escapes Through the Peritoneum of the Intestines During Traumatization*

Time	Mean Blood Pressure, Mm. Hg	Hemoglobin in Blood, per Cent	Chlorides in Blood Plasma, Mg. per 100 Cc.	Chlorides in Fluid, Mg. per 100 Cc.	Sugar in Blood Plasma, Mg. per 100 Cc.	Sugar in Fluid, Mg. per 100 Cc.	Nonprotein Nitrogen in Blood Plasma, Mg. per 100 Cc.	Nonprotein Nitrogen in Fluid, Mg. per 100 Cc.	Total Protein in Blood Plasma, per Cent	Total Protein in Fluid, per Cent
9:30 a.m., control	160	71	587	...	121	...	33	..	5.4	...
11:35 a.m.....	82	...	610	656	166	181	39	41	6.3	4.9
1:35 p.m.....	103	...	620	643	138	163	42	46	6.7	4.9
2:50 p.m.....	90	...	617	633	135	138	48	50	6.7	4.9
3:50 p.m.....	58	106	620	636	133	115	57	60	5.6	5.0

type of experiment presented advantages over the other types studied because the fluid could be obtained from the peritoneal cavity as frequently as desired without making an incision into the injured area. At the termination of the experiment a sample of blood was obtained from the femoral vein for a hemoglobin determination. There was a marked concentration of the blood in all experiments.

There was very little alteration in the chlorides of the blood plasma throughout the course of the experiments. The chloride content of the fluid obtained from the peritoneal cavity was approximately the same as that of the blood plasma obtained at the same time. There were marked alterations in the sugar content of both the plasma and the fluid from the peritoneal cavity throughout the experiments, but the values for both in most instances were approximately the same. The values for nonprotein nitrogen were nearly identical for the samples of plasma and fluid obtained at the same time. There was a progressive rise in the nonprotein nitrogen content of both the plasma and the fluid

throughout the experiments. The total protein of the plasma usually increased slightly during the traumatization but returned to the previous control level after a marked decline in blood pressure had occurred. The total protein content of the plasma was usually slightly greater than that of the fluid.

TABLE 3.—*The Composition of the Fluid that Escapes Through the Peritoneum of the Intestines During Traumatization*

Time	Mean Blood Pressure, Mm. Hg	Hemoglobin in Blood, per Cent	Chlorides in Blood Plasma, Mg. per 100 Cc.	Chlorides in Fluid, Mg. per 100 Cc.	Sugar in Blood Plasma, Mg. per 100 Cc.	Sugar in Fluid, Mg. per 100 Cc.	Nonprotein Nitrogen in Blood Plasma, Mg. per 100 Cc.	Nonprotein Nitrogen in Fluid, Mg. per 100 Cc.	Total Protein in Blood Plasma, per Cent	Total Protein in Fluid, per Cent
9:25 a.m., control	175	76	597	...	151	...	42	..	6.7	...
10:50 a.m.	...	...	...	602	...	363	..	37	...	7.3
11:50 a.m.	106	...	580	557	333	350	37	36	6.5	6.4
12:50 a.m.	130	...	580	569	231	245	37	34	7.3	5.8
3:50 p.m.	116	...	567	590	216	258	40	42	9.8	7.0
5:50 p.m.	54	125	577	552	449	449	58	63	6.9	6.8

TABLE 4.—*The Composition of the Fluid that Escapes Through the Peritoneum of the Intestines During Traumatization*

Time	Mean Blood Pressure, Mm. Hg	Hemoglobin in Blood, per Cent	Chlorides in Blood Serum, Mg. per 100 Cc.	Chlorides in Fluid, Mg. per 100 Cc.	Sugar in Blood Serum, Mg. per 100 Cc.	Sugar in Fluid, Mg. per 100 Cc.	Nonprotein Nitrogen in Blood Serum, Mg. per 100 Cc.	Nonprotein Nitrogen in Fluid, Mg. per 100 Cc.	Total Protein in Blood Serum, per Cent	Total Protein in Fluid, per Cent
10:00 a.m., control	130	84	603	...	111	...	30	..	6.7	...
11:15 a.m.	120	...	...	613	...	150	..	31	...	6.1
12:15 a.m.	120	...	...	619	...	121	..	33	...	5.4
1:15 p.m.	...	...	660	644	90	114	37	33	6.0	5.1
2:15 p.m.	125	...	...	638	...	117	..	35	...	5.0
3:15 p.m.	...	...	...	627	...	108	..	44	...	5.5
4:15 p.m.	108	...	...	607	...	80	..	48	...	5.6
5:15 p.m.	50	112	560	600	60	100	66	60	6.7	6.7

Three of the five experiments are given in tables 2, 3 and 4. The remaining two presented similar results. In two of the three experiments given in the tables the whole fluid and blood were analyzed, while in the remaining experiment the serum alone was used for the analyses.

It is possible that some concentration of the fluid that escaped into the peritoneal cavity resulted from evaporation or absorption. In view of the fact that the fluid was collected frequently, it is believed that this factor is negligible.

3. *Burns.*—Six experiments were performed. The hair was removed by the use of fine clippers or a razor. With the animal deeply anesthetized, a sample of blood was obtained for the control determinations. Approximately one third of the body surface was then burned with soldering irons. The time interval that elapsed between the application of the irons and the reduction of the pressure to the desired level varied

TABLE 5.—*The Composition of the Fluid that Escapes Into the Subcutaneous Tissues After Burns*

Experiment	Time Between Burn and Amputation, Hr.	Control Blood Pressure, Mm. Hg	Blood Pressure Before Amputation, Mm. Hg	Time Sample Was Obtained	Chlorides in Plasma, Mg. per 100 Cc.	Chlorides in Fluid, Mg. per 100 Cc.	Sugar in Blood Plasma, Mg. per 100 Cc.	Sugar in Fluid, Mg. per 100 Cc.	Nonprotein Nitrogen in Blood Plasma, Mg. per 100 Cc.	Nonprotein Nitrogen in Fluid, Mg. per 100 Cc.	Total Protein in Blood Plasma, per Cent	Total Protein in Fluid, per Cent
1	24	142	80	Control, before burning	620 Serum	...	150 Serum	...	25 Serum	...	8.9 Serum	...
				Just before amputation	627 Serum	686	163 Serum	134	70 Serum	62	8.4 Serum	7.6
2	11	170	Dead	Control, before burning	617 Serum	...	88 Serum	...	33 Serum	...	5.2 Serum	...
				Fluid after death	...	633	...	40	...	48	...	6.1
3	14	128	.....	Control, before burning	587	...	132	...	39	...	8.3	...
				Two hours after burning	600	...	130	...	39	...	8.2	...
			Dead	After death	...	643	...	78	...	90	...	7.0
4	15	118	.....	Control, before burning	594	...	142	...	30	...	9.3	...
				Two hours after burning	594	...	148	...	35	...	9.3	...
			Dead	After death	613	627	66	102	126	92	10.2	8.2
5	20	175	.....	Control, before burning	600	...	100	...	30	...	6.8	...
			86	Just before amputation	606	712	125	133	79	79	7.9	5.9
6	17	175	.....	Control, before burning	621	...	181	...	35	...	6.9	...
			57	Just before amputation	643	683	117	133	75	79	8.0	...

from eleven to twenty-four hours in the different experiments. After the blood pressure had reached this level a sample of blood was obtained from the femoral vein. An incision was then made into the inguinal region of the burned side, and a large block of the edematous tissue was removed. Enough fluid for all the analyses was obtained by centrifugating this tissue.

The chloride content of the fluid that was obtained from the subcutaneous tissues was slightly higher in all experiments than was that of the blood plasma. In most experiments the difference in the sugar

content of the fluid and the plasma was not marked. The nonprotein nitrogen content of the plasma was elevated after the burn was produced. In most experiments, values for the nonprotein nitrogen of the fluid and the blood plasma were approximately the same. The total proteins of the blood plasma usually increased slightly following the burns. The total protein content of the blood plasma was usually about 20 per cent higher than that of the subcutaneous fluid.

The results of these experiments are given in table 5.

COMMENT

The relationship between the chloride content of the plasma of the blood and of the fluid that escaped from the blood vessels is such as would be expected from known osmotic laws. The values for the sugar content of the plasma and that of the fluid varied greatly in the different experiments. Cannon [8] found a normal or slightly increased amount of blood sugar in wound shock, while Fabre, Wertheimer and Clogne [9] reported a reduced content of blood sugar. Duval and Grigaut,[10] and Aub and Wu [11] reported an increase in the nonprotein nitrogen of the blood plasma in traumatic shock. Their observations agree with those found in these experiments. It was also found that the nonprotein nitrogen content of the fluid that escapes from the injured vessels is approximately the same as that of the blood plasma. The increase in the nonprotein nitrogen of the plasma is probably due either to tissue destruction or to the decrease in urinary secretion which accompanies the low blood pressure. It is believed that none of these analyses is of major importance in the present study.

As regards the loss of fluid into the injured area in the experiments which have been reported previously,[1] the analyses of particular interest in the present experiments are those of the protein content of the plasma and of the fluid that escaped from the blood vessels at the sites of injury. In most of the experiments the protein content of the fluid that was obtained from the damaged area was nearly identical with that of the blood plasma. The fluids contained in the tissue spaces normally have the same composition in salts as the blood plasma. There is a free interchange of water, salts and substances with a small molecular weight

8. Cannon, W. B.: Acidosis in Cases of Shock, Hemorrhage and Gas Infection, J. A. M. A. **70**:531 (Feb. 23) 1918.

9. Fabre, Wertheimer and Clogne: Quelques considérations sur les modifications humorales et les réactions de l'organisme dans le shock, Bull. et mém. Soc. de chir. de Paris **45**:8, 1919.

10. Duval and Grigaut: L'intoxication par les plaies de guerre: la retention azotée des blessé, Compt. rend. Soc. de biol. **81**:873, 1918.

11. Aub and Wu: Studies in Experimental Traumatic Shock: III. Chemical Changes in the Blood, Am. J. Physiol. **54**:416, 1920.

between the blood stream and the tissue spaces. This is not true of colloids (mainly proteins), as the blood vessels are normally impermeable to them. This is important because the suction force (osmotic pressure) exerted by the plasma proteins normally serves to counterbalance almost exactly the filtration force due to the hydrostatic pressure in the capillaries. This fact was demonstrated by the experiments of Starling [12] and more recently by those of Schade [13] and his co-workers. Schade stated that the edema fluid that occurs in cardiac failure or nephrosis has a very low protein content. A high protein content of edema fluid can be due only to increased capillary permeability and indicates that the trauma must have resulted in severe capillary damage.

In regard to the mechanisms that operate after hemorrhage and after trauma, Cannon [14] stated:

> In normal individuals after hemorrhage, there soon occurs a dilution of the blood due to the passage of fluid from the tissue spaces into the blood stream. The mechanism of this occurrence is explained by Starling as due to such reduction of the blood pressure in the capillaries that the filtration pressure from within them no longer offsets the greater osmotic pressure of the plasma as compared with the lymph, and consequently water passes into the blood stream. It is one of the unexplained features of shock that with the low venous and arterial pressures this process does not occur. Instead, the plasma as a whole makes its escape through the vessel walls.

Studies by Harris and Blalock [15] show very little loss of fluid from the tissues after hemorrhage and only a small fall in the hemoglobin content of the blood. After hemorrhage, the diminished filtration pressure without an increase in the osmotic pressure of the tissue proteins would be expected to cause the passage of some water into the blood stream. This accounts for the small decrease in hemoglobin usually observed. In the types of shock studied in this paper, it seems that the fluid once escaped cannot be reabsorbed to any marked degree because the osmotic pressure in the injured tissue spaces is practically equivalent to that of the blood. The diminution in the capillary pressure probably tends to draw fluid into the blood stream in the noninjured areas. However, if this results, the increase in the mechanical pressure which it causes would tend to cause further loss of fluid into the injured tissues. It is believed that the results of these experiments indicate that the loss of

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12. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, J. Physiol. **19**:312, 1896.

13. Schade, H.: IX. Ueber Quellungsphysiologie und Oedementstehung, Ergebn. d. inn. Med. u. Kinderh. **32**:425, 1929.

14. Cannon, W. B.: Traumatic Shock, New York and London, D. Appleton & Company, 1923, p. 44.

15. Harris and Blalock: Unpublished Observations on the Water Content of the Tissues after Hemorrhage and after Trauma, 1930.

plasma proteins is the most important factor in the production of the low blood pressure after the procedures reported here.

SUMMARY

Studies have been made of the plasma of the blood and of the fluid that escaped from the blood stream at the site of the injury after mild trauma to an extremity, after trauma to the intestines and after burns. The analyses included determinations of the content of chlorides, sugar, nonprotein nitrogen and total protein. The fluid that escaped from the blood vessels of the injured area had approximately the same composition in all of these constituents as the plasma of the blood. Reasons are given for believing that the loss of plasma proteins at the site of injury is the most important factor in the production of shock caused by the experimental methods used in this study.

EXPERIMENTAL SHOCK

IX. A STUDY OF THE EFFECTS OF THE LOSS OF WHOLE BLOOD, OF BLOOD PLASMA AND OF RED BLOOD CELLS *

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In previous experiments,[1] the amount of fluid that was lost from the blood vessels in traumatized areas has been determined. The fluid that escapes from the blood vessels into an extremity as a result of severe trauma consists largely of whole blood. The composition of the fluid that escapes from or into the injured area as a result of mild trauma to an extremity, trauma to the intestines and burns of the body surface was found by Beard and one of us (A. B.)[2] to be nearly identical with that of the blood plasma. These experiments were all performed on dogs anesthetized by barbital. It was believed that the loss of fluid from the blood vessels in the injured area was the chief if not the sole factor in the production of the low blood pressure.

The present experiments were undertaken in order to determine the tolerance of anesthetized dogs to the loss of whole blood or plasma, not into or from the injured area as in the previous experiments, but from a cannula placed in an artery. It seemed that this would give information as to whether or not the reduction in pressure in the previous experiments was due exclusively to the loss of fluid at the site of the trauma. An effort was made to remove the blood or plasma at the same rate as it was probably lost in the earlier experiments. In addition to affording a comparison with the experiments in which trauma was instituted, the present experiments were undertaken in order to determine the specific

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* From the Department of Surgery, Vanderbilt University.

1. Blalock, Alfred: Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury, Arch. Surg. **20**:759 (June) 1930; Trauma to the Intestines: The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure, ibid. **22**:314 (Feb.) 1931; Experimental Shock: VI. The Probable Cause for the Reduction in the Blood Pressure Following Mild Trauma to an Extremity, this issue, p. 598; Experimental Shock: VII. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, this issue, p. 610.

2. Beard, J. W., and Blalock, A.: Experimental Shock: VIII. The Compasition of the Fluid That Escapes from the Blood Stream After Mild Trauma to an Extremity, After Trauma to the Intestines, and After Burns, Arch. Surg., this issue, p. 617.

effects of the removal of whole blood, of blood plasma and of red blood cells.

METHODS

Dogs were used in all the experiments. Sodium barbital, 0.3 Gm. per kilogram of body weight administered intravenously, was employed as the anesthetic. The same anesthetic in identical amounts had been used in the previous experiments in which injury was inflicted. In some of the longer experiments, the barbital was supplemented by morphine sulphate in order to keep the animals quiet. The blood pressure was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. The blood was removed through a cannula in the femoral artery. The hemoglobin was determined at the beginning and end of the experiments by the use of a Sahli hemoglobinometer.

Three types of experiments were performed. In the first group, an amount of whole blood corresponding to 0.5 per cent of the body weight was removed at one hour intervals in some experiments and at six hour intervals in others. In the second group of experiments, an amount of whole blood which equaled 1 per cent of the body weight was removed at one hour or six hour intervals. The blood was defibrinated and centrifugated. The red blood cells plus enough plasma to equal one half of the sample that had been withdrawn were introduced into the external jugular vein. The temperature of the blood at the time of its introduction was approximately that of the body. The interval which elapsed between the removal of the blood and the reintroduction was approximately twenty-five minutes. In the third group of experiments, an amount of whole blood which equaled 1.25 per cent of the body weight was removed at one hour or six hour intervals. The blood was defibrinated and centrifugated. The blood plasma was pipetted off and an amount of plasma equal to 60 per cent of the blood that had been removed was introduced into the external jugular vein. It was necessary to remove more blood in these experiments than in those of the second group because the red blood cells constitute only about 40 per cent of the whole blood. The bleedings were continued in all experiments until death resulted.

In three control experiments, the effects of reintroducing into the circulation blood which had been defibrinated and centrifugated were studied. An amount of whole blood corresponding to 1 per cent of the body weight was removed at one hour intervals until ten bleedings had been performed. The blood was defibrinated and centrifugated and all of it was introduced into the external jugular vein. The blood pressure was approximately the same at the conclusion of these experiments as it was at the beginning, indicating that the defibrinated blood did not produce deleterious effects.

The experimental procedures that were employed in the second and third groups are not exactly comparable to those of the first group because a larger amount of whole blood was temporarily removed, and because the blood was defibrinated and centrifugated before part of it was reintroduced into the circulation. These objections were partially met by performing the experiments that were mentioned in the last paragraph and by experiments similar to those which will be reported for the first group except that whole blood amounting to 1 per cent of the body weight was removed at one hour and six hour intervals, it was defibrinated and centrifugated exactly as in groups 2 and 3, and whole blood equal to one half of the volume which had been removed was reintroduced into the circulation. The results were practically identical with those obtained in group 1, and indicate that the different observations in the three groups of experiments are not due to variations in the experimental methods. The results of these experiments are given in table 1. In some of the experiments in groups 2 and 3, the bleedings

TABLE 1.—*The Effects of Removing at One Hour Intervals and at Six hour Intervals Whole Blood Amounting to 1 Per Cent of the Body Weight, Defibrinating It, Centrifugating It and Reintroducing One Half of the Amount Removed*

Time Between Bleedings	Experiment	Weight of Dog, Kg.	Hemoglobin, per Cent, Control	Amount Bled Each Time, Cc.	First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Seventh Bleeding		Eighth Bleeding		Ninth Bleeding		Tenth Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Bled
					B. P.* Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After		
One hour intervals.....	1	17.0	79	170; replaced 85	135	128	120	100	130	110	116	75	106	67	110	52	96	40	74	Died	...	...	...	...	79	4.5
	2	19.1	95	191; replaced 95.5	120	108	112	102	124	102	120	100	112	110	100	100	94	66	95	55	34	Died	...	...	96	5.0
	3	16.1	106	161; replaced 80.5	138	124	120	120	138	130	124	120	124	115	115	110	120	105	90	30	50	26 Died	...	...	99	5.0
Six hour intervals.....	1	12.5	70	125; replaced 62.5	153	145	130	86	110	68	98	90	100	73	90	80	Died	...	...	...	...	...	...	...	..	3.0
	2	12.5	76	125; replaced 62.5	126	110	138	120	127	120	126	120	130	108	113	80	106	86	92	60 Died	...	...	...	...	81	4.5
	3	9.1	85	91; replaced 45.5	152	152	120	96	120	74	100	73	97	61	90	68	Died	...	...	...	...	...	...	...	87	3.0

* B. P., blood pressure.

were performed twice as frequently and only one-half as much blood was removed each time. The results were approximately the same as in the experiments in which the procedures were not altered.

RESULTS

Group 1. Removal of Whole Blood Amounting to 0.5 Per Cent of the Body Weight.—A, Six Experiments in Which the Bleedings Were Performed at One Hour Intervals: The total amount of blood removed in the different experiments ranged from 3.5 to 6.5 per cent of the body weight. The average of the experiments was 5.1 per cent. The average length of time that elapsed between the first bleeding and death was nine hours and forty-five minutes. In most of the experiments the hemoglobin showed a decline of approximately 14 per cent of that of the control determinations.

The results of these experiments are given in table 2.

B, Six Experiments in Which the Bleedings Were Performed at Six Hour Intervals: The total amount of blood removed in the different experiments ranged from 2 to 4 per cent of the body weight. The average loss was 2.92 per cent of the body weight. The average length of time that elapsed between the first bleeding and death was thirty-one hours and thirty minutes. The hemoglobin was usually decreased by about 9 per cent.

The results of these experiments are given in table 3.

Group 2. Removal of Blood Plasma Amounting to 0.5 Per cent of the Body Weight.—A, Eight Experiments in Which the Bleedings Were Performed at One Hour Intervals: The total amount of fluid removed in percentages of body weight in the different experiments varied from 2.5 per cent plasma and 1 per cent whole blood to 3.5 per cent plasma and 0.85 per cent whole blood. The sum of these figures is 4.05 per cent, which was the average total loss of plasma and whole blood. The figure for the whole blood is necessarily included because the animals died before the red blood cells from the last bleeding had been replaced. The average length of time that elapsed between the first bleeding and death was six hours and thirty-four minutes. The average increase in the hemoglobin was 34 per cent of the control figures.

The results of these experiments are given in table 4.

B, Five Experiments in Which the Bleedings Were Performed at Six Hour Intervals: The total amount of fluid removed in percentages of body weight in the different experiments varied from 2 to 3.5 per cent plasma. The average loss was 2.4 per cent plasma and 0.2 per cent whole blood. The sum of these figures is 2.6 per cent, which was the average total loss of plasma and whole blood. The figure for the whole blood is included because two animals died before the red blood cells

TABLE 2.—*The Effects of Removing Whole Blood Amounting to 0.5 Per Cent of the Body Weight and at One Hour Intervals; No Replacement*

Experiment	Weight of Dog, Kg.	Hemoglobin, per Cent, Control	Amount Bled Each Time, Cc.	First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Seventh Bleeding		Eighth Bleeding		Ninth Bleeding		Tenth Bleeding		Eleventh Bleeding		Twelfth Bleeding		Thirteenth Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Bled
				B. P.* Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After		
1	13.1	75	65	136	124	126	115	140	124	146	128	137	119	120	72	117	73	94	73	86	60	82	Died	...	...	...	...	...	...	..	5.0
2	14.25	..	72	122	108	125	116	137	130	144	135	140	130	134	130	134	129	116	105	90	67	70	42 Died	...	...	...	...	...	...	..	5.0
3	14.0	75	70	160	138	157	147	148	131	145	130	140	120	120	116	114	74	56	54	85	36 Died	...	...	...	...	...	...	...	...	67	4.5
4	11.6	87	58	152	150	158	150	136	140	146	126	150	125	123	108	124	110	118	114	114	105	102	60	72	47	50	30	...	...	73	6.0
5	11.3	78	57	115	100	117	100	113	90	92	58	79	54	56	36	29	19	Died	...	...	...	...	...	...	...	...	...	...	...	65	3.5
6	19.2	85	96	148	148	150	150	154	153	158	150	154	145	150	138	134	126	124	112	118	100	96	92	96	88	87	60	64	37 Died	78	6.5

* B. P., blood pressure.

TABLE 3.—*The Effects of Removing Whole Blood Amounting to 0.5 Per Cent of the Body Weight and at Six Hour Intervals; No Replacement*

Experiment	Weight of Dog, Kg.	Hemoglobin, per Cent, Control	Amount Bled Each Time, Cc.	First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Seventh Bleeding		Eighth Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Bled
				B. P.* Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After		
1	13.0	87	65	156	148	144	144	136	112	56	39	Died	...	...	...	...	...	...	...	..	2.0
2	13.6	87	68	140	125	140	130	138	132	124	115	120	100	Died	...	...	...	...	...	..	2.5
3	8.2	70	41	124	124	126	124	120	120	118	110	106	88	84	86	70	60 Died	...	...	65	3.5
4	8.0	53	40	126	118	117	107	110	108	107	87	112	90	65	50	Died	...	...	...	48	3.0
5	8.4	84	42	132	129	130	130	120	118	114	115	120	118	118	98	104	100	76	63 Died	77	4.0
6	11.75	81	59	158	158	158	140	106	105	88	84	42	29	Died	...	...	...	...	...	..	2.5

* B. P., blood pressure.

TABLE 4.—*The Effects of Removing Blood Plasma Amounting to 0.5 Per Cent of the Body Weight at One Hour Intervals*

TABLE 4.—*The Effects of Removing Blood Plasma Amounting to 0.5 Per Cent of the Body Weight at One Hour Intervals*

Experiment	Weight of Dog, Kg.	Hemoglobin, per Cent, Control	Amount Bled Each Time, Cc.	First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Seventh Bleeding		Eighth Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Bled
				B. P.† Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After		
1	9.95	63	100; replaced 50	143	115	132	75	148	116	146	107	136	92	116	58	Died	...	...	...	68	2.5 plus 1% whole blood
2	8.4	71	84; replaced 42	164	160	160	134	132	110	133	100	114	80	64	Died	...	...	...	...	118	2.5 plus 1% whole blood
3*	13.4	..	77; replacement variable; only cells	120	110	134	105	130	105	120	112	126	88	125	78	130	80	106	50 Died	...	3.55 plus 0.83% whole blood
4	12.9	74	129; replaced 64	145	145	130	120	135	135	140	119	120	75	108	73	106	70	98	50 Died	105	3.5 plus 1% whole blood
5	12.5	80	125; replaced 63	123	102	115	88	115	84	123	100	114	80	100	50	87	38	57	Died	99	3.5 plus 1% whole blood
6*	17.2	..	143; replacement variable	138	132	166	150	165	160	150	146	147	84	130	68	97	42	70	Died	...	3.29 plus 1% whole blood
7	9.3	..	77; replaced 31	114	108	110	90	116	80	100	70	85	56	77	35	67	35	54	Died	...	3.5 plus 1% whole blood
8*	9.55	70	48; replaced 24	154	138	136	116	140	98	140	92	130	87	98	64	100	Died	...	...	92	3.25

* In experiments 3 and 6, the amount removed at each bleeding was approximately, but not exactly, 0.5 per cent of the body weight. In experiment 8, bleedings were performed twice as frequently, and only one-half as much blood was removed each time.
† B. P., blood pressure.

TABLE 5.—*The Effects of the Removal of Blood Plasma Amounting to 0.5 Per Cent of the Body Weight at Six Hour Intervals; Cells Replaced*

Experiment	Weight of Dog, Kg.	Hemoglobin, per Cent, Control	Amount Bled Each Time, Cc.	First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Seventh Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Removed
				B. P.† Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After		
1	10.0	79	100; replaced 50	138	94	120	66	96	56	76	33	Died	...	...	...	...	...	...	2.0
2	8.7	68	87; replaced 43.5	124	108	130	115	115	40	72	32	Died	...	...	...	...	...	86	2.0
3	9.4	81	94; replaced 47	148	125	148	129	130	88	95	85	60	44	Died	...	...	...	106	2.0 plus 0.5% whole blood
4	11.6	81	116; replaced 58	140	130	148	120	135	108	120	64	112	80	102	60	100	65 Died	93	3.5
5*	13.2	66	132; replaced 66	146	120	120	85	108	47	92	67	90	56	45	Died	...	...	81	2.5 plus 0.5% whole blood

* In experiment 5, bleedings were performed twice as frequently and only half as much blood was removed each time.
† B. P., blood pressure.

from the last bleeding had been replaced. The average length of time that elapsed between the first bleeding and death was twenty-eight hours and twenty-four minutes. The average alteration in the hemoglobin was an increase of 24 per cent over the normal.

The results of these experiments are given in table 5.

In two additional experiments, whole blood amounting to 0.83 per cent of the body weight was removed at six hour intervals, and after centrifugation the red cells were replaced in enough saline solution to equal the volume of the blood that had been removed. The plasma was estimated as constituting 60 per cent of the whole blood. In one experiment the loss that produced death was 3.5 per cent plasma and 0.83 per cent whole blood, and in the other experiment 3 per cent plasma and 0.83 per cent whole blood. The total loss that was tolerated was definitely greater than that in the experiments in which the plasma was not replaced by salt solution.

Group 3. Removal of Red Blood Cells Amounting to 0.5 Per Cent of the Body Weight.—A, Six Experiments in Which the Bleedings Were Performed at One Hour Intervals: The total amount of fluid removed in the different experiments in percentages of the body weight varied from 2.5 per cent of red blood cells to 4.0 per cent of red blood cells and 0.63 per cent of whole blood. The average loss was 3.67 per cent red blood cells and 0.52 per cent whole blood. The sum of these figures is 4.19 per cent, which was the average total loss of red blood cells and whole blood. The average length of time that elapsed between the first bleeding and death was seven hours and seventeen minutes. The average alteration in the hemoglobin was a decline of 49 per cent of that of the control determinations.

The results of these experiments are given in table 6.

B, Four Experiments in Which the Bleedings Were Performed at Six Hour Intervals: The loss of fluids in the different experiments varied from 2.5 per cent red blood cells to 2.5 per cent red blood cells and 1.23 per cent whole blood. The average loss in the different experiments was 2.6 per cent red cells and 0.62 per cent whole blood. The average total loss of red cells and whole blood in percentages of body weight was 3.22. The average length of time that elapsed between the first bleeding and death was thirty hours and fifty-three minutes. There was an average decrease in hemoglobin of 30 per cent of the control determinations.

The results of these experiments are given in table 7.

COMMENT

These experiments afford a comparison with those performed earlier,[1] in which the amount of fluid lost from the blood stream in injured

Table 6.—The Effects of Removing Red Blood Cells Amounting to 0.5 Per Cent of the Body Weight at One Hour Intervals

Experiment	Weight of Dog, Kg.	Hemoglobin, per Cent, Control	Amount Bled Each Time, Cc.	First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Seventh Bleeding		Eighth Bleeding		Ninth Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Bled
				B. P.† Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After		
1	9.5	73	117; replaced 71.5	153	148	156	146	154	140	158	140	160	134	146	93	154	77	148	55	Died	...	35	3.5 plus 1.23% whole blood
2	10.9	48	187; replaced 83	117	108	113	92	122	108	110	106	115	105	116	85	106	60	88	50	50	36	25	4.0 plus 0.63% whole blood
3	9.9	82	125; replaced 75	124	90	130	114	134	134	135	128	147	80	136	80	124	74	110	57	39	Died 28	38	4.0 plus 0.63% whole blood
4*	12.6	72	158; replaced 95	146	118	140	92	140	113	148	106	148	90	143	106	130	67	100	38	32	Died	26	4.0 plus 0.63% whole blood
5	11.5	75	145; replaced 87	155	108	110	66	125	85	106	48	96	37	Died	...	...	...	...	...	...	...	48	2.5
6*	9.5	70	60; replaced 36	118	110	116	114	118	120	130	126	138	118	130	90	114	78	105	Died	...	...	41	4.0

* In experiments 4 and 6, bleedings were performed twice as frequently, and only one-half as much blood was removed each time.
† B. P., blood pressure.

TABLE 7.—*The Effects of the Removal of Red Blood Cells Amounting to 0.5 Per cent of the Body Weight at Six Hour Intervals*

Experiment	Weight of Dog, Kg.	Hemoglobin, per Cent, Control	Amount Bled Each Time, Cc.	First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Removed
				B. P.* Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After	B. P. Before	B. P. After		
1	13.55	78	164; replaced 96	153	158	158	140	156	66	132	53	97	40	Died	...	..	2.5
2	15.75	85	196; replaced 117	130	116	170	150	146	108	115	68	97	61	70	34	48	3.0
3	13.85	85	172; replaced 103	160	140	145	104	108	72	98	55	96	64	90	Died 33	68	2.5 plus 1.27% whole blood
4	10.55	72	130; replaced 78	126	116	125	130	126	120	120	85	110	48	100	Died 33	54	2.5 plus 1.23% whole blood

* B. P., blood pressure.

areas had been determined. The experiments in which whole blood amounting to 0.5 per cent of the body weight was removed at one hour intervals correspond roughly to the experiments [3] in which one of the posterior extremities was traumatized severely with a hammer. In the eight experiments reported previously in which one of the posterior extremities was traumatized severely, the average length of time that elapsed between the initiation of the trauma and the reduction of the blood pressure to an average mean of 58 mm. of mercury was three hours and thirteen minutes. The difference in weight of the two extremities equaled 5.3 per cent of the body weight. In the present experiments in which whole blood amounting to 0.5 per cent of the body weight was removed at one hour intervals, the average length of time between the first bleeding and death was nine hours and forty-five minutes. The average loss of whole blood that produced death was 5.1 per cent of the body weight. In these experiments, there was a slight decline in the percentage of hemoglobin, while in the experiments on leg trauma there was a slight rise. This difference is probably due to the loss of a greater proportionate amount of plasma than of red blood cells in the experiments on leg trauma, while whole blood was lost in the present ones.

In twelve experiments on intestinal trauma reported previously,[4] the average length of time between the initiation of the trauma and the reduction of the blood pressure to an average mean of 48 mm. of mercury was five hours. The calculated average loss of fluid from and into the traumatized area was 4.48 per cent of the body weight. The fluid that escaped from the traumatized intestine was found by Beard and one of us (A. B.)[2] to have almost the same composition as the plasma of the blood. In the present experiments in which plasma of the blood amounting to 0.5 per cent of the body weight was removed at one hour intervals, the average length of time between the first bleeding and death was six hours and thirty-four minutes. The average loss of fluid that produced death, expressed in percentages of body weight, was 3.2 per cent plasma and 0.85 per cent whole blood or a total of 4.05 per cent. The slightly larger loss of fluid that was tolerated after trauma to the intestines may be due to the fact that it was lost slowly and continuously while in the experiments employing bleeding, rather large amounts were withdrawn at one hour intervals. The average increase in the hemoglobin above the normal in the experiments on intestinal trauma was 38 per cent and in the experiments on removal of plasma it was 34 per cent.

3. Blalock (footnote 1, first reference).

4. Blalock (footnote 1, second reference).

In ten experiments reported previously in which one of the posterior extremities was only moderately traumatized, the average length of time that elapsed between the initiation of the trauma and the reduction of the blood pressure to an average mean of 33 mm. of mercury was thirty-two hours and sixteen minutes. The average difference in the weight of the two posterior extremities amounted to 3.66 per cent of the body weight. The fluid that accumulated in the traumatized area contained relatively few red blood cells, and its composition was found by Beard and one of us (A. B.)[2] to be approximately the same as that of the blood plasma. In the present experiments in which blood plasma amounting to 0.5 per cent of the body weight was removed at six hour intervals, the average length of time between the initial bleeding and death was twenty-eight hours and twenty-four minutes. The average loss of fluid that produced death, expressed in percentages of body weight, was 2.4 per cent plasma and 0.2 per cent whole blood or a total of 2.6 per cent. The average increase in the hemoglobin above the normal in the four experiments on leg trauma in which it was determined was 27 per cent. In the experiments in which plasma was removed at six hour intervals, the average increase was 24 per cent.

In eighteen experiments reported previously in which part of the body surface was burned, the average length of time that elapsed between the injury and the reduction of the blood pressure to an average mean of 28 mm. of mercury was fourteen hours and thirty-three minutes. The average difference in the weights of the burned and non-burned halves of the body amounted to 3.34 per cent of the body weight. This difference consisted largely of fluid that accumulated in the subcutaneous tissues at the site of the burns. The composition of this fluid was found by Beard and one of us (A. B.)[2] to be approximately the same as that of the blood plasma. There were few red blood cells in it. The duration of the experiments on the effects of burns was intermediate between those in which plasma was removed at one hour and at six hour intervals. As has been stated previously, the total loss of fluid in the experiments in which plasma was removed at one hour intervals was 4.05 per cent of the body weight, and when it was removed at six hour intervals the loss was 2.6 per cent of the body weight. The difference in weight of the two sides of the body (3.34 per cent of the body) is approximately the mean of these two figures. The hemoglobin showed an average increase of 48 per cent above the normal in the nine experiments in which it was determined after burns.

It is interesting to note that the animals that had one extremity moderately traumatized tolerated a slightly greater loss of fluid than the animals that were burned. The duration of the experiments was longer in the instances of trauma of the leg. It may be due to the fact that some red blood cells as well as plasma were lost as a result of traumatiz-

ing an extremity, while burning the part apparently caused a loss of plasma alone. The present experiments show that the loss of whole blood is tolerated better than is the loss of plasma alone. It may be that toxins were partially responsible for the reduction in the blood pressure after the burns. This does not seem likely in these experiments of short duration in which the tolerance to loss of plasma was practically the same after the burns and after the removal of plasma from the femoral artery.

It was found in these and in the previous experiments that an occasional animal dies after only a very small amount of fluid has been lost. It was probably due to the barbital, which is apparently toxic to a small percentage of animals. For example, one animal died after red blood cells amounting to only 1.5 per cent of the body weight had been removed. Two animals died in less than forty-eight hours without the removal of any fluid from the blood stream. However, in the great majority of animals, the blood pressure is not affected markedly by the giving of barbital in the amounts used in these experiments. In studying the effects of severe injury, deep narcosis is necessary, and barbital seems more satisfactory than any other anesthetic that has been tried. As has been stated previously, it was used in the present experiments in order that the results might be compared with those in which trauma was instituted. Otherwise, it is believed that a lighter anesthesia would have been more satisfactory for studying the comparative effects of the loss of whole blood, of blood plasma and of red blood cells.

The results of these experiments show that under the existing circumstances, animals withstand the loss of a greater amount of fluid when the removals are at one hour intervals than at six hour intervals. As has been stated previously, the animals were anesthetized deeply, and they were deprived of food and water. Harris and one of us (A. B.)[5] found that not a great deal of water passes from the body tissues into the blood stream after hemorrhage or trauma under barbital anesthesia. Probably the greater part of this is lost in the expired air, urine and feces.

In the present experiments, dogs usually withstood the loss of a greater amount of whole blood than they did of blood plasma alone or of red blood cells alone. The exception to this was in the experiments in which the removals were performed at six hour intervals when there was a slightly greater tolerance to the loss of red blood cells than of whole blood. The loss of red blood cells alone was tolerated slightly better than was the loss of blood plasma alone. It is believed that the results are comparable because in some experiments in which the effects of the

5. Harris, P. N., and Blalock, A.: Unpublished Observations on the Water Content of the Tissues After Hemorrhage and After Trauma.

loss of whole blood were determined, the blood was defibrinated and centrifugated as in the experiments on the removal of plasma and red blood cells. In several experiments sodium citrate was used as an anticoagulant instead of defibrinating the blood, and the results were approximately the same. In order to remove red blood cells or plasma amounting to 0.5 per cent of the body weight, it was necessary to withdraw temporarily a larger amount of blood than in the experiments on the removal of whole blood. This objection was partially overcome by performing the bleedings twice as often in some of the experiments and removing only one-half as much blood each time. It seems very definite that the loss of red blood cells is tolerated better than the loss of plasma, for it was necessary to remove a larger amount of whole blood in order to be able to leave out of the circulation a given amount of red blood cells than is the case in studying the effects of the removal of plasma. This is true since the plasma constitutes about 60 per cent of the volume of the blood.

SUMMARY

The comparative effects of the removal of whole blood, of plasma and of red blood cells have been determined in thirty-five dogs anesthetized by barbital. The results indicate that the loss of whole blood is usually tolerated better than is the loss in equal amounts of either blood plasma or red blood cells. The animals withstand the removal of a slightly larger volume of red blood cells than of blood plasma.

The results obtained in these experiments have been compared with those reported previously on the effects of severe trauma to an extremity, mild trauma to an extremity, intestinal trauma and burns. They indicate that the cause for the reduction in the blood pressure after the various types of injury was the loss of whole blood or of plasma from the blood stream at the site of the trauma. It does not seem necessary to assume the action of a poison which exerts a general bodily effect.

EXPERIMENTAL SHOCK

X. OBSERVATIONS ON THE WATER CONTENT OF THE TISSUES OF THE BODY AFTER TRAUMA AND AFTER HEMORRHAGE *

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In the normal person or animal, following hemorrhage there occurs a passage of some fluid from the tissue spaces into the blood stream, thereby resulting in a dilution of the blood. Starling [1] believed this to be due to such reduction of the filtration pressure in the capillaries that the osmotic pressure of the plasma proteins is no longer counterbalanced. Cannon [2] stated that it is one of the unexplained features of shock not due to hemorrhage that with the low venous and arterial pressure this process does not occur. Some information in this respect has been reported in previous papers of this series. The amount of whole blood or of plasma that was lost from the blood stream at the site of injury was determined after severe trauma to an extremity,[3] after trauma to the intestines,[4] after mild trauma to an extremity [5] and after burns.[6] Comparison of the figures obtained in these experiments with those found by Johnson and one of us (A. B.)[7] in determining the amount of loss of whole blood and of plasma that produces death in animals anesthetized by barbital indicates that the loss of fluid into the traumatized area was the chief, if not the sole, cause for the decline in the blood pressure. If it is true that the fluid that is lost from the blood stream at the site of

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1. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, J. Physiol. **19**:312, 1896.

2. Cannon, W. B.: Traumatic Shock, New York, D. Appleton & Company, 1923.

3. Blalock, Alfred: Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury, Arch. Surg. **20**:759 (June) 1930.

4. Blalock, Alfred: Trauma to the Intestines: The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure, Arch. Surg. **22**:314 (Feb.) 1931.

5. Blalock, Alfred: Experimental Shock: VI. The Probable Cause for the Reduction in the Blood Pressure Following Mild Trauma to an Extremity, Arch. Surg., this issue, p. 598.

6. Blalock, Alfred: Experimental Shock: VII. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, Arch. Surg., this issue, p. 610.

7. Johnson, G. S., and Blalock, A.: Experimental Shock: IX. A Study of the Effects of the Loss of Whole Blood, of Blood Plasma and of Red Blood Cells, Arch. Surg., this issue, p. 626.

the injury is sufficient to account for the reduction in the blood pressure, there is probably no general increase in capillary permeability with loss of fluid from all of the capillaries of the body. On the contrary, it seems likely that the capillaries in uninjured parts would probably function as do those of the body after hemorrhage in allowing water to pass into them in an effort to increase the volume of the blood. The studies of Beard and one of us (A. B.)[8] show that the fluid that escapes from the blood stream at the site of injury after mild trauma to an extremity, after trauma to the intestines and after burns has approximately the same composition as the plasma of the blood. This observation is of particular importance as regards the content in proteins because the osmotic pressure exerted by the plasma proteins serves to counterbalance the filtration force due to the hydrostatic pressure in the capillaries. It seems likely that the fluid once escaped could not be reabsorbed to any marked degree because the osmotic pressure in the injured tissue spaces is practically equivalent to that of the blood. However, it seems probable that the decrease in capillary pressure resulting from the loss of plasma at the site of the injury would cause some fluid to pass into the blood stream in the uninjured parts of the body. If this results, the increase in capillary pressure that would be caused by the passage of water into the blood stream in uninjured areas would probably cause the further loss of fluid through the injured capillaries.

The present experiments were undertaken in order to determine the water content of the tissues of injured and uninjured parts of the body after trauma to the intestines, trauma to an extremity and burns. For purposes of comparison, the water content of the tissues after the removal of whole blood and of blood plasma from the femoral artery was also determined.

METHODS AND RESULTS

All of the experiments were performed on dogs. The total number of animals used was sixty-seven. They were anesthetized by sodium barbital, which was administered intravenously (0.3 Gm. per kilogram of body weight). The same anesthetic in identical amounts had been employed in the previous experiments on the effects of trauma and hemorrhage. In fact, many of the determinations reported in this paper were performed on tissues obtained from the animals in which other studies on the effects of loss of fluid were being carried out. The blood pressure was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. A Sahli hemoglobinometer was employed in determining the hemoglobin.

Tissues varying in weight usually from 1 to 2 Gm. were placed in small beakers, the weight of which had been determined previously. By the use of a small pair of sharp scissors, the tissues were cut into many pieces. This was done in order to facilitate the drying. The weight of the beaker plus the tissue

8. Beard, J. W., and Blalock, A.: Experimental Shock: VIII. The Composition of the Fluid That Escapes from the Blood Stream After Mild Trauma to an Extremity, After Trauma to the Intestines and After Burns, Arch. Surg., this issue, p. 617.

was determined. They were then placed for approximately 48 hours in an oven, the temperature of which was kept at as nearly 105 degrees centigrade as possible. At the end of this time, they were again weighed. From these figures, the content of the tissues in water or in solids was determined.

Two different types of experiments were performed.

Group 1.—In the first group of experiments, the percentage in solids of the various tissues was determined in normal animals and in those in which a low blood pressure had been produced by mild trauma to an extremity, by trauma to the intestines and by burning part of the body surface. Analyses were performed on tissues from the liver, lung, kidney, intestine, heart muscle, brain, spleen and skeletal muscle. In the experiments on trauma to an extremity, skeletal muscle was obtained from the traumatized as well as the nontraumatized side. In the experiments on burns, in addition to the other tissues, samples were taken from the subcutaneous tissues of both the burned and nonburned areas and from the skeletal muscle of both the injured and noninjured parts. In all instances, the piece of skeletal muscle was removed from one of the flexor muscles of the thigh and the heart muscle was obtained from the left ventricle. The subcutaneous tissues were removed from the inguinal region. The specimens of brain tissue were taken from the cerebrum. They included both white and gray matter, the water content of which is different, and the results were probably of little value. Attempts were made to obtain blocks of brain tissue of the same thickness in each experiment.

The results that were obtained in all of these experiments are given in table 1.

It is to be seen that there is a good deal of variation in the individual figures for the experiments of the control group as well as the others. The most significant observation is that the average of the figures for the same organ is approximately the same for the control experiments as for those in which a low blood pressure had been produced by injury. Leaving out of consideration the determinations on the tissues that were traumatized, the greatest variation between the averages for the different tissues in the control group and those after the three varieties of injury is that the content in solids of the skeletal muscle was 2.3 per cent higher after mild trauma to an extremity than was the average figure for the control group. In no other instance was the average difference as much as 2 per cent. In practically all instances, the average figure for solids was slightly higher for the experiments in which the blood pressure was low than in the control experiments.

In the experiments on trauma to one extremity, the muscle of the injured side had a lower percentage of solids than muscle from the opposite normal extremity. On the contrary, muscle obtained from an extremity the skin of which had been burned had a higher percentage of solids usually than muscle from the opposite extremity. The sub-

cutaneous tissues of an area that had been burned had a content in water several times as great as that of subcutaneous tissue from other parts of the body. The traumatized intestine had a slightly lower average percentage of solids than was found for the intestines in the control experiments.

Obviously, comparisons are not entirely satisfactory in which the control determinations and the experiments proper are performed on

TABLE 1.—*The Percentage in Solids of the Tissues After the Various Procedures*

				Percentage of Solids											
Procedure	Experiment	Mean Blood Pressure, Mm. Hg.	Percentage Increase in Hemoglobin	Liver	Lung	Kidney	Intestine	Heart	Brain	Spleen	Muscle	Muscle of Traumatized Side	Subcutaneous Tissue	Subcutaneous Tissue of Burned Side	Duration of Experiment, Hr.
Normal controls	1	...	..	26.1	21.7	23.2	27.4	22.9	24.0	22.0	28.3	....	....	....	..
	2	...	..	....	21.3	22.1	26.5	22.1	26.0	23.7	31.6	....	....	....	..
	3	...	..	26.0	20.4	20.8	21.1	20.7	20.0	21.0	26.5	....	....	....	..
	4	...	..	26.4	20.5	22.2	22.0	20.7	24.9	20.9	24.6	....	....	....	..
	5	...	..	28.7	20.0	20.8	20.7	21.4	24.9	21.7	24.7	....	....	....	..
	6	...	..	27.2	21.0	20.0	20.8	21.9	23.2	22.5	25.3	....	....	....	..
	7	...	..	25.5	19.6	21.1	19.8	21.6	24.0	20.6	24.7	....	....	....	..
	8	...	..	28.5	22.3	20.5	22.8	22.2	23.3	22.2	31.4	....	....	....	..
		Averages		26.9	20.9	21.3	22.7	21.7	23.8	21.8	27.1				
Mild leg trauma	1	105	12	26.9	21.6	24.6	25.4	24.3	21.0	21.3	26.8	26.6	....	....	47
	2	56	26	....	23.4	22.4	24.4	24.5	22.9	22.4	31.4	23.9	....	....	50
	3	72	11	26.9	22.2	23.4	26.8	23.3	24.3	22.2	34.3	25.7	....	....	23
	4	...	..	24.1	19.2	19.1	22.6	22.6	23.3	21.6	20.2	20.3	....	....	38
	5	...	..	26.1	20.3	20.0	25.8	23.6	....	22.4	34.1	25.9	....	....	30
	6	60	45	26.6	20.6	20.0	23.8	....	22.4	21.5	25.2	18.7	....	....	18
	7	95	38	25.4	21.9	21.7	23.5	21.9	24.7	21.7	33.9	25.1	....	....	31
	8	41	12	26.5	22.8	24.6	24.3	23.7	25.4	22.8	....	27.0	....	....	25
	9	87	31	26.4	22.8	21.6	23.0	23.8	23.9	21.8	....	25.0	....	....	31
	10	49	27	26.4	23.5	24.1	24.8	22.4	23.7	25.1	....	30.3	....	....	22
		Averages		26.1	21.8	22.6	24.4	23.3	23.5	22.3	29.4	24.9			
Intestinal trauma	1	58	..	27.8	23.2	25.6	20.9	22.8	24.0	....	26.9	....	....	....	6
	2	10	..	27.0	24.5	21.4	23.1	23.8	26.6	22.2	28.2	....	....	....	7
	3	...	6	27.4	21.9	21.3	24.3	21.8	21.3	20.6	27.4	....	....	....	5
	4	58	33	27.7	22.0	20.8	20.5	22.9	28.9	22.8	27.4	....	....	....	7
	5	49	64	28.6	23.1	22.3	20.8	23.0	26.7	22.9	27.7	....	....	....	8
	6	56	49	26.8	21.8	22.3	20.0	22.6	22.8	21.1	27.2	....	....	....	6
		Averages		27.6	22.8	22.3	21.6	22.8	25.1	21.9	27.5				
Burns	1	78	..	27.0	23.4	22.1	24.4	22.1	23.4	....	25.5	29.8	85.3	30.0	11
	2	50	..	28.2	23.1	23.5	23.9	25.7	25.1	24.2	30.5	30.4	71.8	18.0	11
	3	...	..	26.2	21.3	22.1	23.4	23.2	20.8	23.8	25.0	27.2	72.3	16.1	17
	4	...	..	25.1	21.7	21.3	23.5	....	23.4	23.8	29.9	29.9	63.7	13.7	14
	5	...	38	26.5	22.7	22.1	21.7	22.5	21.7	22.4	24.3	24.6	46.6	10.7	16
	6	75	40	25.9	24.2	22.1	26.0	23.0	22.7	21.3	29.6	29.4	79.5	21.7	24
	7	...	..	....	....	....	....	....	....	....	25.7	26.3	75.2	22.3	22
		Averages		26.5	22.7	22.2	23.8	23.3	22.9	23.1	27.2	28.2	70.6	18.9	

different animals. If tissues are to be taken from parts of the body such as the heart and lungs, it is necessary that different animals be used. Since the muscles and skin contain more than 50 per cent of the water of the body, experiments were performed in which samples of muscle, skin and blood were obtained before and after the various procedures.

Group 2.—In the second group of experiments, the percentage in solids or in water of the blood, skeletal muscle and skin was determined before and after the various procedures. Eight different types of experi-

ments were performed. The total number of experiments was thirty-six. The samples of blood were removed from the femoral veins. Muscle and skin were removed from symmetrical parts of the body at the beginning and end of the experiments. In the greater number of experiments, the samples of muscle were from the two pectorals. In some experiments, the specimens were removed from one of the flexor muscles of the two forearms.

In the first five experiments, the animals were anesthetized by barbital, and specimens were taken for analysis. After periods of time varying from twenty-six to forty-seven hours, the second samples were removed. No water or food was given and these experiments were used simply as controls for the other experiments in which procedures in addition to the giving of barbital were carried out. The blood pressure remained the same or fell slightly during the period of observation. The average increase in hemoglobin was 18 per cent of the control reading. The average content in solids of the blood rose from 18.1 to 20 per cent, of the muscle from 23.6 to 25.6 per cent and of the skin from 37.1 to 39.2 per cent.

In the next five experiments, whole blood amounting to 0.5 per cent of the body weight was removed from the femoral arteries of dogs at one hour intervals until death resulted. Specimens of blood, muscle and skin were obtained at the beginning of the experiments and after the blood pressure had fallen to a low level. The mean blood pressure at the time the second series of samples were obtained varied from 20 to 64 mm. of mercury. The average decrease in the hemoglobin was 14.6 per cent of the control figures. The average content in solids of the blood declined from 19.5 to 18.4 per cent. The content in solids of the muscle increased from 24.7 to 25.2 per cent, and that of the skin from 41.5 to 44.4. The increase in the percentage of solids of the muscle was less than that found in the control experiments. However, the control experiments were of longer duration.

In the next five experiments, whole blood amounting to 0.5 per cent of the body weight was removed from the femoral arteries at six hour intervals until the animals died. The samples were obtained before the first bleeding and after the blood pressure had been reduced to a low level. The level of the mean blood pressure at the time that the second series of samples were obtained varied from 0 to 63 mm. of mercury. The average decrease in hemoglobin was 8 per cent of that of the control period. The content in solids of the blood was changed from 19.1 to 19.5 per cent, that of the muscle from 24.5 to 25.2 per cent and that of the skin from 45.8 to 49.5 per cent. There was a smaller increase in the percentage of solids in the muscle in these experiments than in the control experiments in which simply the effects of prolonged barbital anesthesia were determined. The alterations in the skin and muscle

were approximately the same as in the experiments in which the bleedings were at one hour intervals.

In the succeeding four experiments, blood plasma equal to 0.5 per cent of the body weight was removed at one hour intervals until death resulted. Samples were obtained before the first removal of the plasma and shortly before the termination of the experiments, at which time the mean blood pressure varied from 15 to 50 mm. of mercury. The average increase in hemoglobin was 36 per cent of the figures for the control periods. The content in solids of the blood was altered from 19.1 to 23.2 per cent, that of the muscle from 25.1 to 26.5 per cent, and that of the skin from 48.7 to 46.8 per cent.

In the next four experiments, blood plasma amounting to 0.5 per cent of the body weight was removed at six hour intervals until the animal died. Samples were obtained at the beginning and shortly before the termination of the experiments, at which time the mean blood pressure varied from 0 to 57 mm. of mercury. The average percentage in hemoglobin was 24 per cent higher at the termination of the experiments. The average content in solids of the blood was altered from 19.3 to 22.1 per cent, that of the muscle from 24.6 to 25.1 per cent and that of the skin was practically unchanged.

In the succeeding four experiments, the effects of mild trauma to an extremity on the content in solids or in water were determined. The interval of time that elapsed between the initiation of the trauma and the reduction of the blood pressure to the desired level varied from twenty-two to thirty-one hours. Specimens of blood, muscle and skin were obtained before the institution of the trauma and after the mean blood pressure had been reduced to levels varying from 42 to 90 mm. of mercury. The average percentage in hemoglobin was 23 per cent higher at the termination of the experiments than at the beginning. The average content in solids of the blood was increased from 19.4 to 23.6 per cent, that of the muscle from 25.3 to 26.5 per cent, and that of the skin decreased from 36 to 35 per cent. The alteration in the content of solids of blood and muscle was slightly greater in these experiments than in those in which blood plasma was removed at six hour intervals. The duration of the two types of experiments was approximately the same.

In the next four experiments, the effects of trauma to the intestines were studied. The time that elapsed between the beginning of the trauma and the reduction of the pressure to the desired level varied from two hours and thirty minutes to seven hours. Specimens of blood, muscle and skin were obtained before the initiation of the trauma and after the mean blood pressure had been reduced to levels varying from 32 to 57 mm. of mercury. The average percentage in hemoglobin was 48 per cent higher at the termination of the experiments than at the beginning. The average content in solids of the blood was altered from 20.1 to 22.8 per cent, that of the muscles from 24.3 to 25.5 per cent and

that of the skin from 40.4 to 40.7 per cent. The alteration in the content of solids of the muscle was approximately the same as in the experiments in which plasma was removed at one hour intervals. The duration of the two types of experiments was approximately the same.

In the succeeding four experiments, the effects of burns were studied. The time that elapsed between the beginning and the end of the experiments varied from fourteen to twenty hours. The mean blood pressure at the time the second series of samples were obtained varied from 0 to 86 mm. of mercury. The average content in solids of the blood changed from 21.5 to 23.8 per cent, that of the muscle from 26.8 to 28.3 per cent, and that of the skin from 42.0 to 49.1 per cent. The alteration in the percentage of solids of the muscle was the same as that in the experiments in which plasma was removed at one hour intervals and approximately the same as that found in the experiments in which an extremity or the intestines were injured.

The results of all of these experiments are given in table 2.

The percentage alterations in the average amount of solids of the blood, muscles and skin that were produced by the various procedures are given in table 3.

TABLE 2.—*The Percentage in Solids of Blood, Muscle and Skin Before and After the Various Procedures*

Procedure	Experiment	Time Samples Were Obtained	Mean Blood Pressure, Mm. Hg.	Hemoglobin per Cent	Per Cent in Solids			Comment
					Blood	Muscle	Skin	
Controls: effects of barbital anesthesia and water deprivation	1	Control	137	90	17.2	21.7	31.2	46 hours between samples
		End of experiment	96	73	19.4	22.8	34.0	
	2	Control	160	70	19.0	24.1	38.9	47 hours between samples
		End of experiment	168	82	20.0	25.7	44.5	
	3	Control	145	66	19.0	22.0	28.7	46 hours between samples
		End of experiment	116	78	20.6	22.4	30.0	
	4	Control	148	66	17.0	25.2	34.3	46 hours between samples
		End of experiment	148	78	20.8	24.8	39.5	
	5	Control	122	66	18.4	25.2	52.5	26 hours between samples
		End of experiment	92	74	19.3	27.6	48.2	
	Averages	Control	...	...	18.1	23.6	37.1	
		End of experiment	...	...	20.0	25.6	39.2	
Removal of whole blood, 0.5%, every hour	1	Control	136	...	20.6	26.5	43.8	5% of body weight
		End of experiment	20	...	20.5	26.3	44.0	
	2	Control	160	75	19.4	26.2	43.4	4.5% of body weight
		End of experiment	64	67	17.0	27.0	49.0	
	3	Control	122	...	15.5	22.4	30.5	5% of body weight
		End of experiment	44	...	....	22.8	31.1	
	4	Control	152	87	20.0	23.9	35.2	5% of body weight
		End of experiment	64	73	19.5	24.2	41.6	
	5	Control	115	78	18.1	24.4	52.8	3% of body weight
		End of experiment	36	65	16.4	25.5	56.1	
	Averages	Control	...	...	19.5	24.7	41.5	
		End of experiment	...	...	18.4	25.2	44.4	
Removal of whole blood, 0.5%, every six hours	1	Control	140	87	21.5	25.1	44.0	2.5% of body weight
		End of experiment	Dead	...	....	26.7	46.1	
	2	Control	156	87	22.0	26.6	43.8	2% of body weight
		End of experiment	10	...	24.5	25.9	43.5	
	3	Control	126	53	15.3	22.1	60.4	3% of body weight
		End of experiment	50	48	15.0	24.0	64.4	
	4	Control	124	70	17.8	24.8	38.5	3.5% of body weight
		End of experiment	60	65	17.5	24.1	46.6	
	5	Control	139	84	21.1	24.1	42.5	4% of body weight
		End of experiment	63	77	21.1	25.2	47.0	
	Averages	Control	...	...	19.1	24.5	45.8	
		End of experiment	...	...	19.5	25.2	49.5	

TABLE 2.—*The Percentage in Solids of Blood, Muscle and Skin Before and After the Various Procedures—Continued*

Procedure	Experiment	Time Samples Were Obtained	Mean Blood Pressure, Mm. Hg.	Hemoglobin per Cent	Per Cent in Solids			Comment
					Blood	Muscle	Skin	
Removal of plasma, 0.5%, every hour	1	Control	143	63	17.2	23.8	46.4	2.5% plus 1% whole blood
		End of experiment	50	68	18.7	24.4	45.6	
	2	Control	164	71	20.0	24.4	45.4	2.5% plus 1% whole blood
		End of experiment	15	118	24.3	25.3	42.5	
	3	Control	123	74	19.8	25.0	53.9	3.5% plus 1% whole blood
		End of experiment	42	105	24.7	25.6	53.8	
	4	Control	145	80	19.4	27.3	49.2	3.5% of body weight
		End of experiment	50	99	25.2	30.5	45.4	
	Averages	Control	...	...	19.1	25.1	48.7	
		End of experiment	...	...	23.2	26.5	46.8	
Removal of plasma, 0.5%, every six hours	1	Control	124	68	16.9	24.0	55.1	2% of body weight
		End of experiment	45	86	20.2	24.5	58.3	
	2	Control	138	79	....	22.9	55.9	2% of body weight
		End of experiment	...	...	....	23.6	59.1	
	3	Control	148	81	21.1	....	50.0	2% plus 0.5% whole blood
		End of experiment	20	106	24.9	....	54.9	
	4	Control	140	81	20.8	27.7	51.0	3.5% of body weight
		End of experiment	...	93	22.4	28.0	41.7	
	5	Control	145	66	18.2	23.6	50.7	2.5% of body weight
		End of experiment	57	81	20.8	24.2	48.3	
	Averages	Control	...	...	19.3	24.6	65.7	
		End of experiment	...	...	22.1	25.1	65.6	
Leg trauma	1	Control	140	103	22.3	28.4	40.3	25 hours between trauma and termination
		End of experiment	42	115	25.2	27.3	28.4	
	2	Control	145	68	19.2	23.8	31.3	31 hours between trauma and termination
		End of experiment	90	89	23.4	28.3	37.3	
	3	Control	160	88	21.3	26.0	46.2	22 hours between trauma and termination
		End of experiment	48	112	26.2	28.0	42.4	
	4	Control	130	53	14.7	22.8	26.2	22 hours between trauma and termination
		End of experiment	61	68	18.6	22.3	31.7	
	Averages	Control	...	...	19.4	25.3	36.0	
		End of experiment	...	...	23.6	26.5	35.0	
Intestinal trauma	1	Control	165	76	20.1	25.6	47.0	Trauma of 7 hours' duration
		End of experiment	49	125	24.2	27.7	52.1	
	2	Control	160	71	19.1	26.1	46.1	Trauma of 5 hours' duration
		End of experiment	57	106	22.8	27.2	37.2	
	3	Control	116	62	19.7	21.1	29.2	Trauma of 2½ hours' duration
		End of experiment	40	70	17.6	21.8	27.5	
	4	Control	140	85	21.3	24.5	39.3	Trauma of 3½ hours' duration
		End of experiment	32	135	26.6	25.4	45.8	
	Averages	Control	...	...	20.1	24.3	40.4	
		End of experiment	...	...	22.8	25.5	40.7	
Burns	1	Control	165	78	21.2	26.7	42.5	14 hours between burn and death
		End of experiment	...	...	22.5	28.9	55.8	
	2	Control	120	57	18.8	26.0	49.7	16 hours between burn and death
		End of experiment	...	...	18.5	27.1	52.5	
	3	Control	158	...	22.6	26.6	34.1	20 hours between burn and termination
		End of experiment	86	...	27.9	28.5	40.0	
	4	Control	160	...	23.4	28.0	41.7	17 hours between burn and termination
		End of experiment	60	...	26.1	28.6	48.1	
	Averages	Control	...	...	21.5	26.8	42.0	
		End of experiment	...	...	23.8	28.3	49.1	

TABLE 3.—*The Percentage Alterations in the Average Per Cent in Solids of Blood, Muscle and Skin That Were Produced by the Various Procedures*

Procedure	Percentage Alterations		
	Blood	Muscle	Skin
Control experiments on barbital	+10.5	+8.5	+5.7
Removal of whole blood, 0.5%, every hour	— 5.6	+2.0	+7.0
Removal of whole blood, 0.5%, every 6 hours	+ 2.1	+2.9	+8.1
Removal of plasma, 0.5%, every hour	+21.5	+5.6	—3.9
Removal of plasma, 0.5%, every 6 hours	+14.5	+2.0	.....
Mild leg trauma	+21.6	+4.7	—2.8
Intestinal trauma	+13.4	+4.9	+0.7
Burns	+10.7	+5.6	+16.9

COMMENT

The analyses of particular interest in these experiments are those on the skeletal muscle. Volkmann [9] stated that 50.8 per cent of the total water of the body tissues is in muscle. Durig [10] found in animals deprived of water that all of the organs do not lose weight to the same extent. The brain loses the least weight, next comes the kidney, with the heart, liver and muscle increasing in order. Engels [11] studied the effects of the administration of sodium chloride on the water content of the various tissues of the body. He used as his controls dogs that had received neither food nor water for four days. After administration of fluids, the muscles increased in weight more than any other tissues except the kidneys. The blood showed the least increase. Of the total amount of water taken up by the tissues of the body, 68 per cent was absorbed by the muscle. Bidder and Schmidt,[12] Bischoff,[12] Volkmann [12] and Voit [12] showed that the skin and muscles not only contain the highest percentage of water, but that they are also the greatest reservoirs for water in the body. In experimental diarrhea produced by magnesium sulphate or senna, Tobler [13] found that from 25 to 30 per cent of the body weight was lost in a few days, and that skin and muscle suffered 65 per cent of the loss. In his review on anhydremia, Marriott [14] stated: "The body possesses an available store of water which exists for the greater part in the muscles and in the skin, and which can be drawn upon to some extent before any considerable degree of desiccation of other parts of the body occurs." The determinations on the skin in the present experiments are probably almost valueless, because it was impossible to be sure in all instances that all of the fat had been removed from its under surface. Fatty tissues contain very little water, and hence any alterations in the amount of fat that was left attached to the skin would change the percentage in water of the sample.

The various procedures produced surprisingly small alterations in the content in solids of skeletal muscle and likewise of all other tissues that were analyzed. The change in the percentage of solids of the skeletal muscle was greater in the experiments in which the animals were anesthetized by barbital and deprived of food and water for periods varying from twenty-six to forty-seven hours than in the experiments

9. Volkmann, A. W., quoted by Engels (footnote 11).

10. Durig, A.: Wassergehalt und Organfunction, Arch. f. d. ges. Physiol. **85**:401, 1901.

11. Engels, W.: Die Bedeutung der Gewebe als Wasserdepots, Arch. f. exper. Path. u. Pharmakol. **51**:346, 1904.

12. Quoted by Tobler (footnote 13).

13. Tobler, L.: Zur Kenntnis des Chemismus akuter Gewichtsstuerge, Arch. f. exper. Path. u. Pharmakol. **51**:346, 1904.

14. Marriott, W. McKim: Anhydremia, Physiol. Rev. **3**:275, 1923.

in which injury was instituted or in those in which whole blood or plasma was removed. It has been shown by Beard and one of us (A. B.)[8] that the fluid that is lost from the blood stream at the site of injury after mild trauma to an extremity, after trauma to the intestines and after burns has approximately the same composition as the plasma of the blood. There was a loss of plasma in the experiments in which whole blood was removed from the femoral artery. It is mainly the proteins of the blood plasma which maintain the osmotic pressure in the capillaries and serve to counterbalance the filtration force due to the hydrostatic pressure. When plasma is lost from the blood stream as a result either of trauma or of hemorrhage, there is a decrease in the colloids of the circulating blood and hence a lowering of the total osmotic pressure. In view of this, it is not surprising that there is apparently such a small amount of water that passes into the blood stream. The results of these experiments indicate that the same mechanisms operate after hemorrhage and after trauma. They are probably different in degree in that the osmotic pressure in the capillaries is lowered more by the loss of plasma than by the removal of the same amount of whole blood. Associated with trauma is injury to the capillaries, which allows not only water but colloids to pass through their walls. The loss of large amounts of plasma causes a diminution in the capillary pressure and this probably tends to allow fluid to pass into the blood stream in noninjured parts of the body just as in hemorrhage. If this takes place, the increase in pressure in the capillaries probably causes further loss of fluid into the injured area. It is probably for this reason that shock due to trauma is usually more difficult to treat than that due to uncomplicated hemorrhage. After hemorrhage, it is usually simply a matter of restoring the blood volume after the bleeding vessels have been ligated. After trauma, any procedure that increases the hydrostatic pressure in the vessels tends to cause the further loss of fluids through the injured capillaries.

As has been stated previously, the amount of water that left the tissues for the blood stream in these experiments was not great. If it is assumed for the moment that the amount of water that passed from all tissues of the body into the blood stream equalled 2 per cent of the body weight, and this figure does not seem low in view of the present observations, this would represent 200 cc. in a dog weighing 10 Kg. In experiments of the duration of the average experiment reported here, the greater part of the water would be lost in the expired air and a smaller proportion in the urine and feces.

It is of interest that whereas there was usually a slight diminution in the amount of water in the uninjured tissues of the body, there was an increase in the content in water of the damaged tissues. It is believed that this is strong evidence against the possible action of toxic products which produce a general increase in capillary permeability. It is also of

interest that whereas the subcutaneous tissues of a burned area had a great increase in their content in water, the muscle beneath the injured area had a slightly lower content in water than muscle from the opposite nonburned side.

It is believed that these experiments emphasize the importance of the plasma proteins in maintaining a normal blood volume. They indicate that only a small amount of water leaves the tissues for the blood stream when there has been a considerable reduction of the blood plasma.

SUMMARY

The content in water and solids of various tissues of the body has been determined in control experiments and in those in which a low blood pressure had been produced by trauma and burns. The animals were all anesthetized by barbital and were not given water or food during the experiments. There was little difference in the content in water or solids of the tissues in the control experiments and in those in which injury had been inflicted.

In additional experiments, the content in water and solids of blood, muscle and skin was determined before and after a low blood pressure had been produced by the removal of whole blood, by the removal of blood plasma, by mild trauma to an extremity, by trauma to the intestines and by burns. The results were compared with those obtained in experiments in which the animals were simply given barbital and left on the table for periods of time varying from twenty-six to forty-seven hours. The analyses of particular importance were those on the muscles, because they contain the greater part of the water in the body. There was a larger loss of water by the muscles in the control experiments than in those in which hemorrhage or injury was studied.

Reasons are given for the belief that hemorrhage and trauma are similar in that in each there is a loss of plasma proteins with a diminution in the total osmotic pressure. After trauma, there is a larger proportional loss of blood plasma and hence a relatively greater diminution in the osmotic pressure. The decrease in the colloids explains the inability of the blood stream to attract more water from the tissues. The main factor which is most likely responsible for the continued low blood pressure after injuries is not a general increase in capillary permeability with loss of fluid all over the body, but a loss of blood plasma through the walls of the damaged capillaries.

THE ABSORPTION OF DEXTROSE FROM THE COLON

II. A STUDY OF THE EFFECTS OF CHEMICAL EXCITANTS AND OF STIMULANTS ON DEXTROSE ENEMA *

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Results obtained by us [1] previously in experiments carried out on dogs indicate that a 5 per cent aqueous solution of dextrose is not absorbed from the colon to any appreciable extent. Tap water and physiologic solution of sodium chloride are rapidly and efficiently absorbed. As a control in those experiments we exposed the ileum simultaneously to the same solutions in the same dog by using the same technic, and variable but considerable absorption was observed.

This study was continued in order to observe the fate of dextrose in enemas made up of equal parts of 5 per cent solution of dextrose and solutions of various chemicals that might possibly act as excitants or stimulants to absorption. The fact that a 0.9 per cent solution of sodium chloride was readily absorbed by the large bowel suggested that salt might favor the absorption of dextrose when the two substances are mixed in proper proportions.

Goldschmidt [2] and Fantus [3] informed us that the presence of sodium chloride in the intestine increases the absorption of other substances. Sodium bicarbonate is another chemical commonly used by surgeons in postoperative enemas. Clendenning [4] stated that sodium bicarbonate and brandy are both beneficial adjuncts to rectal administration. Bab-

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* These experiments were carried out in the Physiological Laboratory of Northwestern University Medical School, under Dr. A. C. Ivy, head of the Department of Physiology.

1. McNealy, R. W., and Willems, J. D.: The Absorption of Glucose from the Colon: A Preliminary Study of the Glucose Enema, Surg. Gynec. Obst. **49**:794, 1929.

2. Goldschmidt, S.: On the Mechanism of Absorption from the Intestine, Physiol. Rev. **1**:421, 1921.

3. Fantus, Bernard: The Technic of Medication, Chicago, American Medical Association, 1926.

4. Clendenning, Logan: Modern Methods of Treatment, St. Louis, C. V. Mosby Company, 1928.

kin [5] reported that the activity of the gastro-intestinal tract is markedly increased and may even be doubled by the presence of alcohol.

Our experiments in this study were made in order to determine what effect, if any, sodium chloride, sodium bicarbonate and ethyl alcohol might exert on the absorption of a dextrose solution from the colon of the dog. Attention was focused mainly on the nutrient value of the sugar enema and less on the mechanism of absorption. Incidentally, however, it was impossible to disregard entirely some interesting effects that these substances seem to exert on the intestinal mucosa and on the liver. These incidental effects will be considered only briefly in this paper, since we regard that part of the problem as open for further investigation.

METHODS AND TECHNIC

Dogs were used in these experiments as in our previous work. They were prepared and the experiments were carried out exactly as before [1] with two minor alterations in the details.

In the first place the solution to be absorbed was allowed to remain in the ileum and colon for one hour instead of one and one-half hours. This was done because we have found that the maximum rates of absorption in the dog's intestines, large and small, are reached usually in about from twenty to thirty minutes after the solutions are introduced, and that in about one hour the rate of absorption is usually diminishing. Our curves for blood sugar demonstrate this fact. It is interesting to note also that in several instances more than 70 cc. of fluid were taken up in one hour by a loop of ileum approximately 18 inches (45.72 cm.) in length. Professor Verzar [6] finds that about 16 cc. of water per minute are taken up by the human intestine, or, roughly speaking, about 0.5 cc. per foot (30.48 cm.) per minute. In many of our experiments this rate of absorption was greatly exceeded by the ileum.

Secondly, another control check was run on the blood sugar by taking in all instances samples of blood from the femoral vein for determinations of sugar in addition to samples from the mesenteric veins of the colon and the ileum. This sample of blood from the femoral vein is representative of the blood sugar content of the general systemic circulation, and is of considerable interest and importance in our interpretations.

Three groups of experiments were performed. In the first group six dogs were used. We mixed equal quantities of solutions of 5 per cent dextrose and 0.9 per cent sodium chloride. We have shown [7] in an earlier report that the optimum concentration of a dextrose solution, or any other solution that is introduced into the body, is that concentration with the same osmotic tension as a

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5. Babkin, B. P.: Die aeussere Sekretion der Verdauungsdruesen, ed. 2, Berlin, Julius Springer, 1928.

6. Verzar, Professor of Physiology, University of Budapest, Hungary, in a lecture on absorption from the intestine given at Northwestern University Medical School, Oct. 8, 1929.

7. Willems, J. D., and McNealy, R. W.: Glucose Solution: Its Optimum Concentration for Therapeutic Administration, Northwest Med. **28**:329, 1929.

physiologic solution of sodium chloride. A 4.5 or 5 per cent dextrose solution is iso-osmotic with a 0.9 per cent salt solution. By beginning with two isotonic solutions, all mixtures of the two in any proportions whatever will still remain at the same osmotic level and be isotonic with the blood and the tissue fluids. The mixture that we used in this group contained 2.5 per cent dextrose and 0.45 per cent sodium chloride. Such a mixture is physiologically normal, and is most likely to be absorbed if absorption of these substances in the colon does take place. Our endeavor was to establish the most favorable circumstances for absorption.

After proper preparation of the narcotized animal, blood samples were withdrawn from three points: the femoral vein, the mesenteric vein of the colon and the mesenteric vein of the lower end of the ileum. Accurately measured quantities of the dextrose-salt mixture, usually 75 cc. were then placed into each of the isolated bowel loops by the methods that we[1] have described in our preliminary report. Twenty minutes later and forty minutes later, samples of blood were again withdrawn from the same places previously mentioned. One hour after the introduction of the solutions their residues were removed, accurately measured and titrated by Benedict's quantitative method for dextrose. Sugar determinations were made on the samples of blood by the Folin and Wu colorimetric method. In both of these procedures it was important that one develop a certain facility and accuracy of technic before the determinations could be called completely reliable, and the marginal error was reduced to a definite constant minimum.

From the figures obtained for the mixed solutions in the intestinal loops, graphs were plotted (of which charts 1, 3 and 5 are typical examples) showing in terms of cubic centimeters the amounts of solution introduced and removed after one hour's exposure to the absorptive possibilities of the bowels, and showing also the amounts of dissolved dextrose introduced and removed in terms of grams. From the figures representing the blood sugar values in the nine samples of blood, graphs were made showing the levels of the blood sugar in the femoral vein and in the mesenteric veins of the ileum and of the colon. Charts 2, 4 and 6 are representative of these graphs. All the charts here reproduced are paired, each pair being made from the same animal in the course of one experiment. Therefore they show conclusively what happened, so far as the sugar is concerned, within the lumen of the bowels and in the blood.

The second group of experiments covers three dogs and differs from the first only in that the substances used were equal quantities of 5 per cent solution of dextrose and 1.5 per cent solution of sodium bicarbonate. From the standpoint of the molecular weight and the freezing point depression of sodium bicarbonate, such a concentration is practically physiologically normal. Charts 3 and 4 are from a typical experiment of this type.

The third group involves four dogs. A mixture of 5 per cent dextrose and 6 per cent ethyl alcohol was used. The experiments were carried out as before. No unified idea exists among authors as to the strength of alcohol that will give optimal results physiologically. From 1 to 12 per cent has been used. A concentration of about 0.75 per cent in the blood stream is required before serious damage results to the blood. With such vague information for a starting point, we decided on a 3 per cent strength of alcohol for this particular type of experiment. The results were quite definite, as will be shown later.

Mention should be made here that we have made no effort to determine the fate of the exciting substances other than the dextrose in the intestines. Nor do we know the amounts of sodium chloride, of sodium bicarbonate or of alcohol that were present in the residual solutions.

EXPERIMENTAL RESULTS

Examination of the charts, which are from typical experiments of each group, will give the clearest idea of the results. Charts 1 and 2 represent dog T, a male, weighing 43 pounds (19.5 Kg.). Seventy-five

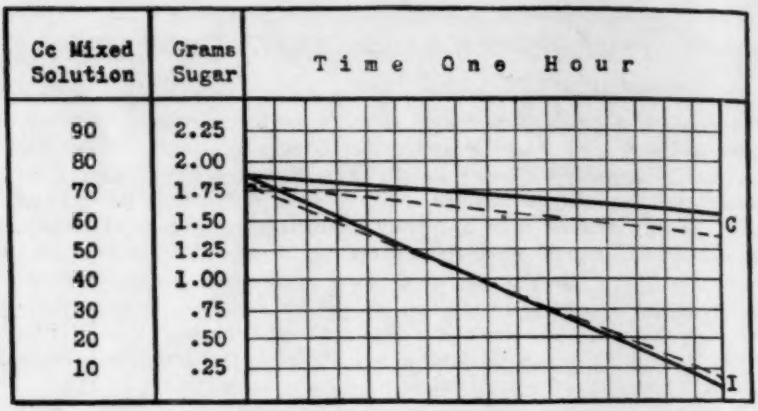

Chart 1.—Absorption of a dextrose-saline enema from the colon, *C*, and the ileum, *I*. The solid lines represent the solution; the broken lines, dextrose. The left hand column shows the amount of solution in cubic centimeters; the next column, the amount of dextrose in grams.

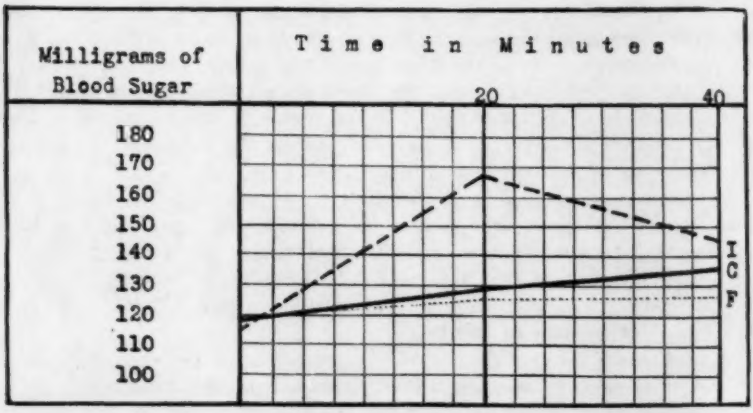

Chart 2.—Blood sugar levels, before and after the administration of the dextrose-saline enema, in the colic vein, *C;* ileal vein, *I;* and femoral vein, *F*. The column of figures is the scale on which the blood sugar level is measured.

cubic centimeters of the dextrose-salt mixture, containing 1.79 Gm. of dextrose, was introduced quantitatively into each bowel loop. From the ileum we removed 4 cc. of residual solution containing 0.14 Gm. of dextrose; from the colon, 62 cc. containing 1.37 Gm. of dextrose. From

the ileum, 71 cc. of solution, and 1.65 Gm. of dextrose were absorbed; from the colon, 13 cc. and 0.42 Gm. A glance at the graphs will aid considerably in visualizing these figures.

Chart 2 shows the observations on the blood sugar in the same experiment. At the beginning of the experiment, the blood sugar values

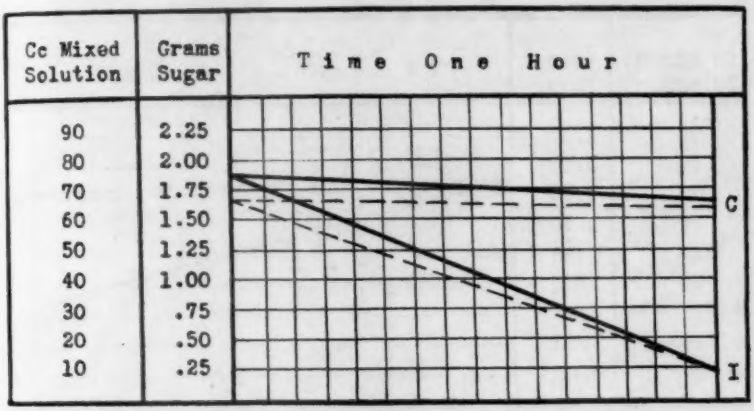

Chart 3.—Absorption of a dextrose-sodium bicarbonate enema from the colon, *C*, and the ileum, *I*. The solid lines represent solution; the broken lines, dextrose.

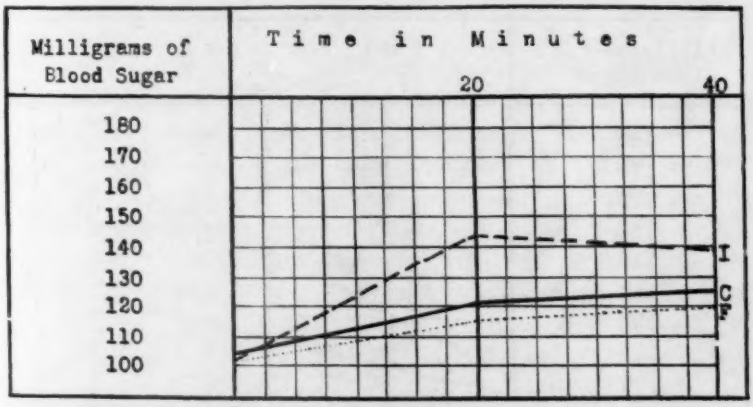

Chart 4.—Blood sugar levels, before and after the administration of dextrose-sodium bicarbonate enema, in the colic vein, *C;* in the ileal vein, *I;* and in the femoral vein, *F*.

are seen to be as follows: *C*, 119 mg.; *I*, 115 mg.; *F*, 120 mg. In twenty minutes these values are, respectively, 129, 166 and 126 mg. At forty minutes, they are 135, 145 and 127 mg. Again a glance at the chart will make clear the meaning of these figures. It shows that there is an obvious reciprocal relation to the observations recorded in chart 1.

Charts 3 and 4 are those for dog Y, a female, weighing 36 pounds (16.3 Kg.). In this case 75 cc. of dextrose-sodium bicarbonate mixture was introduced, in which there was contained 1.68 Gm. of dextrose. One hour later we removed from the ileum 9 cc. of solution together with 0.22 Gm. of dextrose; from the colon 65 cc. and 1.58 Gm. of

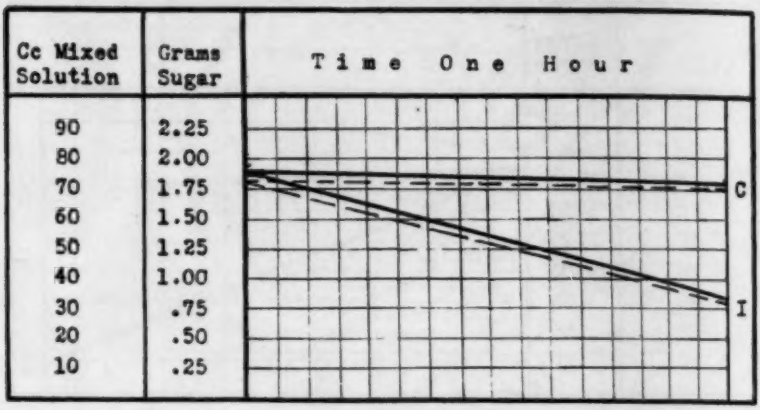

Chart 5.—Absorption of a dextrose-alcohol enema from the colon, *C*, and from the ileum, *I*. The solid lines represent the solution, the broken lines, dextrose.

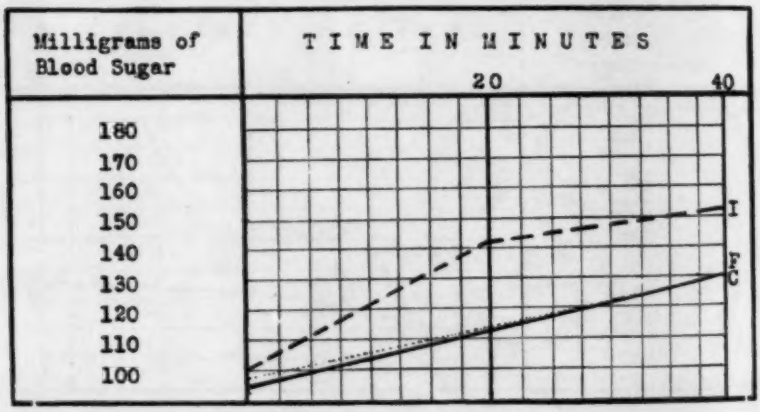

Chart 6.—Blood sugar levels, before and after the administration of dextrose-alcohol enema, in the colic vein, *C;* in the ileal vein, *I;* in the femoral vein, *F*.

dextrose. The blood sugar values at the outset were: *C*, 104 mg.; *I*, 102 mg.; *F*, 102 mg. At the twenty minute period there were, respectively, 121, 143 and 115 mg.; at the forty minute period, 125, 139 and 119 mg.

Charts 5 and 6 show graphically what occurred in dog W, a male, weighing 40 pounds (18.1 Kg.). In this experiment 75 cc. of dextrose-alcohol mixture was used, containing 1.86 Gm. of dextrose. There remained in the ileum at the end of the experiment 32 cc. of the solution, containing 0.79 Gm. of dextrose; in the colon, 71 cc. containing 1.78 Gm. The blood sugar values in this experiment were as follows: First samples, *C*, 96 mg.; *I*, 100 mg.; *F*, 97 mg.; twenty minute samples, *C*, 112 mg.; *I*, 141 mg.; *F*, 113 mg.; forty minute samples, *C*, 130 mg.; *I*, 152 mg., and *F*, 130 mg.

COMMENT

When we worked out our earlier results [1] with an aqueous solution of dextrose, we were surprised to note that the colon absorbed practically no sugar. We had expected at least a slight absorption. The redoubling of our efforts at accuracy and the elimination of marginal errors only duplicated our observations. When we used tap water or physiologic solution of sodium chloride, it was found that the colon absorbed these substances rapidly. In fact, the colon absorbed salt solution more efficiently than water and did it better than, or as well as, the ileum. Therefore, it appeared interesting to know how the colon would handle a mixture of such an excitant as sodium chloride and such a deterrent as dextrose. Obviously, if conditions within the colon could be kept physiologically as nearly normal as possible and the solutions isotonic, one of the three substances, namely, water, dextrose or excitant, or any two of them, or even all three of them, might possibly be absorbed. But—in the words of that peer among modern physiologists, Claude Bernard—why think and wonder when one can experiment and know?

When 75 cc. of any solution is introduced into the colon and removed without any absorption taking place, about 95 per cent of the solution can be recovered. About 5 per cent is unavoidably lost in the process of transfer. It is probably safe to state that a loss of more than 5 per cent means absorption. Approximately the same figures hold for the dextrose. In chart 1, it is shown that 17.5 per cent of the fluid and 22 per cent of the dextrose were lost from the colon. This loss was undoubtedly due to absorption. Although the actual amount absorbed was small, it was, nevertheless, too great to be regarded as experimental error.

Dextrose, when absorbed from the colon, can be satisfactorily demonstrated in the portal blood of the vein draining the colon. Once this blood traverses the liver, considerable change may take place. One of the main functions of the liver is the regulation of the blood sugar level in the general systemic circulation. In the process of ingestion of dextrose by the bowel, the blood sugar level in the portal blood rises

higher than in the systemic blood; at no time in a physiologically normal procedure can the reverse condition occur. A rise in the blood sugar of the portal blood may be the secondary result of a rise in the general systemic blood sugar, or it may be due to absorption of sugar from the intestine. Indeed, the blood sugar can rise in the colic vein for at least three reasons: absorption of dextrose from the colon, absorption from the ileum which raises the general blood sugar, or because of some change or changes in the liver which releases stored glycogen into the general circulation as dextrose. From any rise in blood sugar in the colic vein must be subtracted the value of the blood sugar in the femoral vein taken at the same moment. The remainder represents the true rise in the colic vein due to absorption of dextrose from within the colon. It was this line of reasoning that showed us the necessity of establishing the general level for systemic blood sugar in the femoral vein each time that any other blood sugar value was taken.

With these points in mind, an examination of chart 2 is exceedingly interesting. At the beginning all three graphs are at approximately the same level, the slight differences being due to unavoidable experimental errors. Then there is a marked rise in the broken line *I*, followed by a less marked decline after absorption in the ileum has reached its peak. The sugar absorbed by the ileum has, to some extent, raised the general level of the blood sugar, because there is a rise in the dotted line *F* as well. The rise in *F* is reflected in the solid line *C*, which has also risen. But the rise in the graph *C* is greater than that in *F*, and that difference can be accounted for only by an actual rise in the blood sugar of the colic vein, due to the absorption of dextrose from the colon. The quantity of dextrose absorbed is small, but we have found it repeatedly present in the dextrose-salt experiments. Thus this rise in the blood sugar in this experiment accounts for the loss of dextrose shown in chart 1. It seems plain, then, that the presence of the sodium chloride in this mixture caused the colon to absorb small but definite quantities of dextrose.

In the experiments with dextrose-sodium bicarbonate a slight loss of water is seen in chart 3, but practically no loss of dextrose from the colon. This observation is borne out by the blood sugar curves in chart 4, which show a marked rise in the ileal vein and a parallel rise in the colic and femoral veins, which is simply a rise in the general circulation. There is here no progressive divergence of the graphs *C* and *F* as in chart 2. They remain practically parallel. It is evident that the rise in *C* is merely a reflection of the rise in *F*, and that both are secondary to the rise in *I*. Thus it can be said that there is practically no absorption of dextrose from this mixture in the colon.

In the dextrose-alcohol experiments, as seen in chart 5, there is again no appreciable loss of dextrose from the colon. But the blood sugar levels (see chart 6) rise rapidly in all three curves.

Applying our previous method of reasoning to these observations, we came to the conclusion that the alcohol, reaching the liver probably by way of the ileum, caused some change or changes in that organ which resulted in a marked general hyperglycemia. The nature of this change is not entirely clear. It may be a breaking down of the barrier of the liver to the increase of sugar in the portal blood; or, more likely, a liberation of dextrose from the stored glycogen in the liver, since the increase of the dextrose in the blood is probably greater than can be accounted for by the absorption of the 1.07 Gm. lost from the ileum. The conclusion seems entirely warranted that alcohol has no demonstrable effect on the absorption of dextrose from the colon. But when the alcohol reaches the liver by way of the ileum, it produces there some change or changes, resulting in a rather sudden marked hyperglycemia.

It is self-evident that experiments of this nature cannot be carried out on human patients. We expect to continue with this work on dogs, and ultimately to adapt the problem in a modified form to the human colon.

SUMMARY AND CONCLUSIONS

1. A 5 per cent solution of dextrose is not absorbed from the colon to any appreciable extent.

2. Tap water and physiologic solution of sodium chloride are rapidly and efficiently absorbed by the colon.

3. A small amount of dextrose can be absorbed from the colon from a dextrose-saline mixture. The sodium chloride influences the absorption of the dextrose.

4. Dextrose is not appreciably absorbed from the colon from a dextrose-sodium bicarbonate mixture.

5. Practically no dextrose is absorbed from the colon when a dextrose-alcohol mixture has been injected. The absorption of the alcohol causes a hyperglycemia in a short time.

6. There is no evidence to show that the dextrose enema is of any practical nutritional value.

CORRELATION OF FUNCTION WITH CAUSE OF DEATH FOLLOWING EXPERIMENTAL INTESTINAL OBSTRUCTION AT VARYING LEVELS*

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Following complete obstructions of the upper part of the intestine in the dog, life may be prolonged for three or four weeks in a large number of such animals when saline is administered subcutaneously. If the administration of saline is interrupted after five or six days, the animals will often live as long as when saline is administered daily until the death of the animal.[1] When saline is not administered, death usually occurs within three or four days, and an elevation of the blood urea, decrease of the plasma chlorides and an increase in the combining power of the blood for carbon dioxide occur. The administration of saline precludes the development of these chemical changes in the blood. The saline serves as an effectual antidote, not for a toxin absorbed, but for the essential fluids lost by vomiting.

When obstruction is established in the descending colon of a dog, the animal usually survives for a considerable period and, apparently, dies of starvation. Occasionally, death occurs in the first week following such experimental obstruction; we have had two animals that died on the forty-second and fiftieth days postoperatively, following the establishment of obstructions by severing the lower part of the colon.[2]

When obstruction is established in the lower part of the ileum, dogs survive for a longer period (usually from five to seven days) than do animals with similar obstructions in the duodenum. However, saline does not afford them the protection exhibited by animals with duodenal

* Submitted for publication, June 9, 1930.

* From the Department of Surgery, University of Minnesota.

1. Hausler, R. W., and Foster, A. C.: Studies on Acute Intestinal Obstruction, Arch. Int. Med. **36**:31 (July) 1925. Wangensteen, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction: III. Simple Obstruction: A Study of the Cause of Death in Mechanical Obstruction of the Upper Part of the Intestine. Arch. Surg. **16**:1242 (June) 1928.

2. Wangensteen, O. H., and Lynch, F. W.: Evaluation of X-Ray Evidence as Criteria of Intestinal Obstruction, Proc. Soc. Exper. Biol. & Med. **27**:674, 1930.

obstruction. The length of life of animals with complete ileal obstructions is little greater after the subcutaneous administration of saline than when this is omitted. There is at present no satisfactory explanation for the cause of death in simple obstruction of the ileum.

TABLE 1.—*Anastomosis of Colon to Stomach*

Dog*	Initial Weight, Kg.	Terminal Weight, Kg.	Post-operative Duration of Life, Days	Subcutaneous Administration of Saline (400 Cc. of 1% Solution), Days	Blood Chemistry
1	13.9	8.6	22	0	Essentially normal
2	18.9	10.7	33	0	Essentially normal
3	9.3	8.6	6	0	Essentially normal
4	25.0	16.8	17	0	Terminal CO_2 combining power, 73
5	29.3	14.5	30	0	Essentially normal
6	13.0	9.1	20	0	Essentially normal
7	10.0	7.5	17	2	....
8	7.9	7.5	9	4	....
9	12.0	8.6	38	3	Essentially normal

Average 21.3 days

* A fecal impaction just proximal to the anastomosis constituting a simple obstruction occurred in several of these animals.

TABLE 2.—*Anastomosis of the Ileum to the Stomach*

Dog	Initial Weight, Kg.	Terminal Weight, Kg.	Post-operative Duration of Life, Days	Subcutaneous Administration of Saline (400 Cc. of 1% Solution), Days	Blood Chemistry
1	17.7	14.3	8	5	Terminal (blood urea nitrogen, 114.8; chlorides, 181.5)
2	15.5	10.7	24	4	Essentially normal
3	14.3	11.4	5	0	Essentially normal
4	20.5	11.8	56	0	Terminal (blood urea nitrogen, 58.8; chloride, 165)
5	17.0	11.4	26	0	Normal blood urea nitrogen and chloride
6	21.8	17.3	16	0	Normal blood urea nitrogen and chloride
7	16.6	....	33	0	....
8	25.9	18.2	18	0	....
9	21.8	....	6	1	....
10	15.7	....	16	0	Normal chlorides and blood urea nitrogen
11	11.0	8.3	11	3	Normal chorides and blood urea nitrogen

Average 19.9 days

There exists a high degree of correlation between embryology, blood supply and function in the intestine. The stomach, duodenum (as far as the papilla of Vater) and the pancreas develop from the foregut. Liberal amounts of digestive secretions are furnished by these organs. Their source of blood supply is the celiac axis. The remainder of the

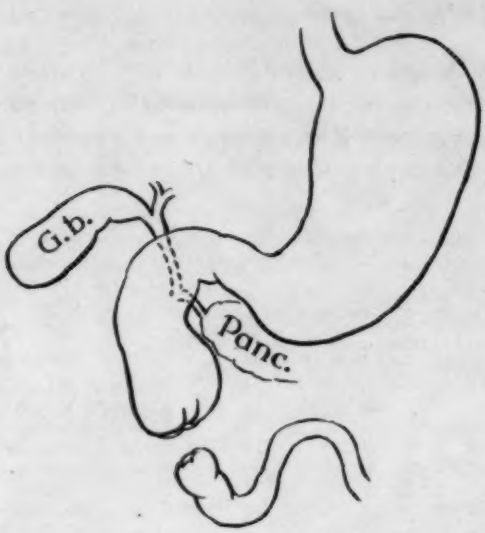

Fig. 1.—High intestinal obstruction. The blood chemistry is as follows: high blood urea, low plasma chlorides, alkalosis (high carbon dioxide combining power). Saline is an antidote for fluid lost by vomiting.

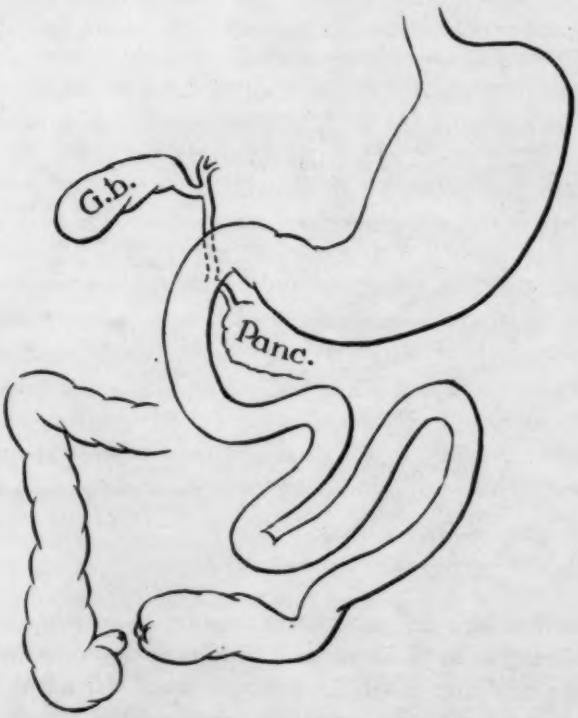

Fig. 2.—Low ileal obstruction. There is no alteration in the blood chemistry; the cause of death is uncertain. Saline is not specific.

small intestine to the midportion of the transverse colon develops from the midgut, receives its blood supply from the superior mesenteric artery, and has to do with absorption. The remainder of the colon develops from the hindgut, receives its blood supply from the inferior mesenteric artery, and has excretion as its function. In a dog with obstruction low in the colon, the acute obstruction features are frequently absent because the obstruction is beyond the absorptive area

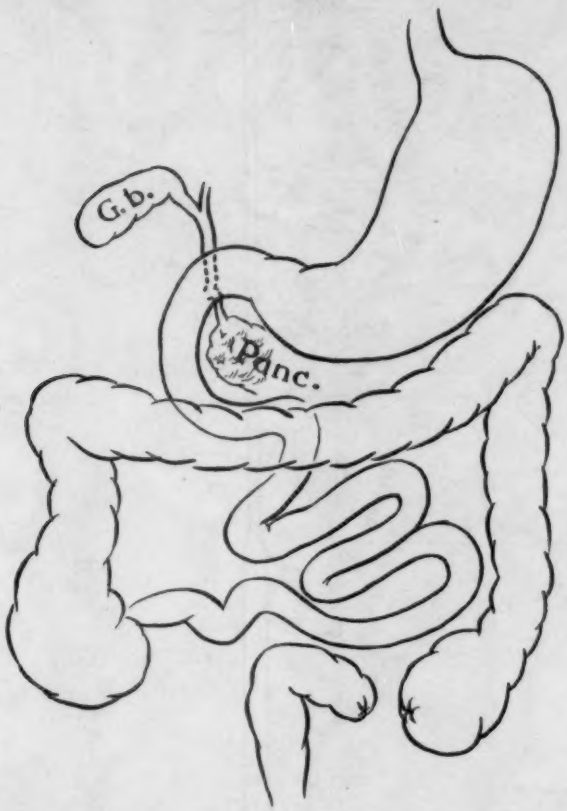

Fig. 3.—Obstruction in the lower portion of the colon. There is no alteration in the blood chemistry. The animal dies of starvation or of acute obstruction.

and the accumulation within the bowel is not as great as when the absorptive area is blocked out. Post mortem, such dogs exhibit considerable emaciation. Fecal masses are solidly impacted above the inverted end of the bowel. In those dogs that survive obstruction of the colon for only a short period, interference with absorption due to edema and other changes in the proximal wall of the bowel probably

occurs, permitting distention and acute obstructive phenomena to dominate the picture. When the obstruction is established in the lower part of the ileum in the midabsorptive area of the intestine, the picture of acute obstruction and distention predominates.

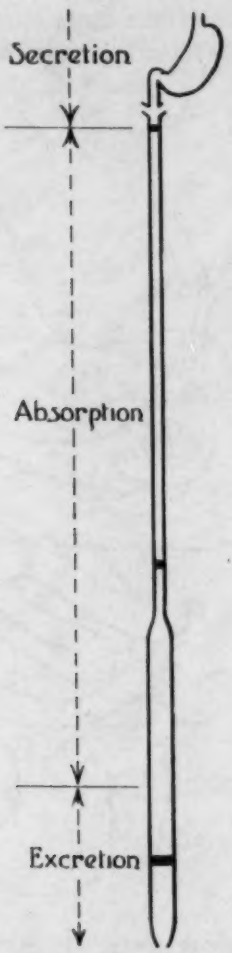

Fig. 4.—Intestinal tract conceived of as a long straight tube in which the dark lines represent obstructions at the levels already described in the three previous figures. The important factors are: (1) loss of essential fluids by vomiting; (2) absorption; (3) distention, especially as related to the blood supply.

In explaining the death of an animal with this type of obstruction, the intestine may be conceived of as a long tube with obstruction in the midabsorptive area. Only the fluid at the upper end can be vomited, the lower portion being more or less continuously full and distended.

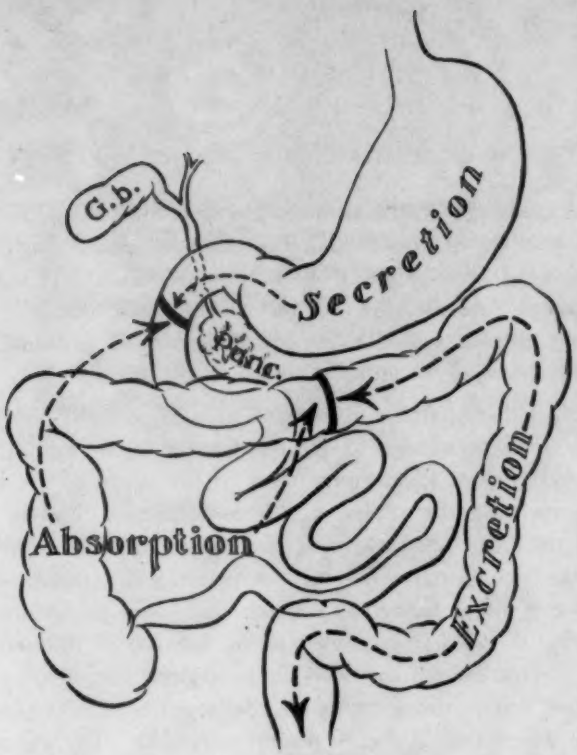

Fig. 5.—Schematic drawing to illustrate the relation of function in the intestinal tract to the types of obstruction already described.

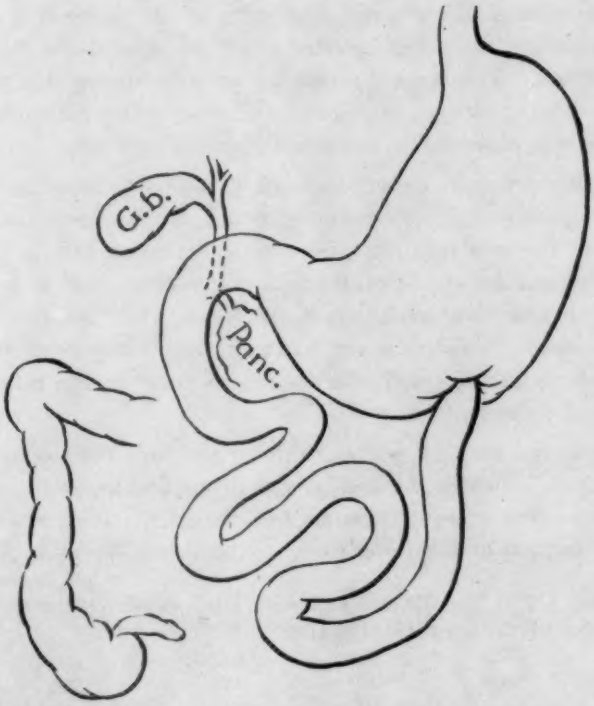

Fig. 6.—Anastomosis of the terminal ileum to the stomach in which the distal end of the ileum is inverted. This is also an obstruction with only the oral end open, but with the distal ileum opening into the stomach, from which point its content can easily be evacuated by vomiting.

With the increasing accumulation of gas and fluid in such a long tube, the lower reaches of the occluded segment probably partake of the characteristics of strangulation obstruction in which deprivation of the blood supply and necrosis of the wall of the bowel obtain. The ileum also has not as rich a blood supply as have more proximal segments of the small intestine.[3]

On the premise that the absorptive area is partially blocked out in ileal obstructions, permitting of greater damage to the wall of the bowel, we have anastomosed the terminal end of the ileum to the side of the stomach, permitting the return of the accumulated fluid in the lower reaches of the obstructed segment to the stomach, from which point it is more easily vomited. Such an obstruction was established in eleven dogs. (A few other animals in which this same procedure was performed were excluded from consideration because of the occurrence of peritonitis.) One animal survived the procedure fifty-six days and was in fairly good health, though vomiting daily until the fifth postoperative week, from which time a steady decline occurred. The average period of survival was 19.9 days. Studies of the blood chemistry were made on the animals in this group; with the exception of the blood of dogs 1 and 4, in which there was a terminal rise of blood urea and decrease of blood chlorides, the blood was normal.

In nine other dogs the terminal portion of the descending colon was severed, the distal end being inverted and the proximal end anastomosed to the stomach. The longest period of survival among this group was thirty-three days, with an average of twenty-one and three-tenths days. No change was observed in the blood chemistry values.

In another group of experiments an attempt was made to determine whether a preliminary enterostomy would not prolong the survival period after the establishment of simple obstruction low in the ileum, it being assumed that the ileum would accommodate itself to the absorption of water following exclusion of the colon, which apparently occurs in human beings. Unfortunately, however, dogs stand ileostomy poorly and are poorer risks for experiments on intestinal obstruction than are other normal animals.

The increased survival period (ninteen and nine-tenths days) in the group of dogs in which the end of the ileum was anastomosed to the stomach over that observed (from five to seven days) in dogs with simple obstruction in the lower part of the ileum serves to emphasize

3. Morton, J. J.: The Difference Between High and Low Intestinal Obstruction in the Dog, Arch. Surg. **18**:1119 (April) 1929.

the significance of the mechanical factors (length of tube and blocked absorption) in the cause of death in low ileal obstructions. Roentgenograms of the abdomen of dogs with several ileal obstructions did not uniformly demonstrate the accumulation of large amounts of gas and fluid in the proximal loops; but greater opportunity for injury of the mucosa would appear to obtain in low ileal obstructions than is observed in duodenal obstructions because of the greater length of the peristaltic rushes.

A REVIEW OF UROLOGIC SURGERY

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(Concluded from p. 526)

URETER

Calculi.—Cathcart [27] reported a case of ureteral stone of unusual size and weight. A man, aged 48, had had appendectomy for severe pain in the right side of the abdomen. During convalescence the same type of pain continued as before operation. Two years later a diagnosis of right ureteral stone was made, and after two attempts the stone was successfully removed. Five years later the abdominal pain again appeared on the right side. For six months the patient had had an uncomfortable, heavy feeling in the right lower portion of the abdomen. A roentgenogram of the kidney and urinary bladder revealed a shadow extending from the transverse process of the third lumbar vertebra to the wall of the bladder. At operation the kidney was freed from its bed and the pedicle was ligated and left loose in the wound. Through a right lower abdominal incision the ureter was cut off close to the wall of the bladder, and the kidney and ureter were delivered. The kidney was practically destroyed; it was hydronephrotic and infected secondarily. There was marked dilatation and infection of the ureter which contained the stone. The entire specimen of kidney, ureter and stone weighed 290 Gm.

In the literature there were only four reports of cases of unusually large ureteral stone. The stone varied in length from 7.5 to 19 cm.

27. Cathcart, Edward: Ureteral Stone of Unusual Size, Proc. Staff Meet., Mayo Clin. **5**:117 (April 30) 1930.

and in weight from 44 to 54 Gm. The largest stone measured 19 cm. in length and weighed 52 Gm. The stone in the case reported by Cathcart measured 19 cm. in length and weighed 90 Gm.

Deaver and Burden [28] reviewed 113 cases of the stone in the ureter. In 66 instances operation was performed, and in 47 treatment was carried out by cystoscopic methods. In 98 of the cases the stone was in the lower part of the ureter, a position favorable for cystoscopic manipulation unless certain contraindications are present.

A stone that has remained for a considerable time in the upper part of the ureter, usually at the ureteropelvic juncture, is firmly fixed, obstructs the passage of a catheter, causes rapid and progressive impairment of renal function and is not amenable to cystoscopic manipulation. Removal of the obstruction should be by ureterolithotomy or by pyelolithotomy. A stone seldom lodges in the middle third of the ureter; if it is in this position the procedure for its removal depends on the acuteness of the symptoms and the condition of the kidney above it. Surgical removal of a stone in this position, although a little more difficult to perform, is preferable to cystoscopic manipulation.

Before removing a ureteral stone surgically, it is essential to know: (1) that an accurate diagnosis has been made; (2) the urologic status of the opposite kidney; (3) that coexistent extra-urinary disease has been eliminated or taken into consideration, and (4) that sufficient preoperative preparation has been carried out. In the event of certain complications in the removal of a stone from the ureter, particularly postoperatively general surgical training is of decided advantage in restoring the patient to health. Ureterolithotomy through an extraperitoneal approach is the operation of choice for stone in the ureter. To approach the upper third of the ureter, the incision is made in the loin, as for nephrectomy. This incision permits possible manipulation of the stone back into the pelvis of the ureter from which its removal may be accomplished with less trauma than from the ureter proper, and renders the kidney available for inspection. The incision may be extended to care for a stone in the middle third of the ureter. The latter may be approached through an incision to the lateral side of the rectus muscle when it is necessary to be more careful in working down toward the ureter by displacing the peritoneum toward the median line. It should be remembered that the ureter is often closely adherent to the peritoneum and, in the dissection, is carried forward with it. Access to the lower part of the ureter may be obtained through an incision to the lateral side of the rectus muscle or by an incision just

28. Deaver, J. B., and Burden, V. G.: The Surgical Management of Stone in the Ureter, Ann. Surg. **91**:85 (Jan.) 1930.

above Poupart's ligament. In this position the peritoneum is easily reflected and the base of the bladder is exposed. Manipulation may be difficult because of the depth of the wound. The ureter should be identified and traced down to its juncture with the bladder. When the stone has been located, it is preferable to work it into another position in the ureter, so that the longitudinal incision for its removal will not be placed in the inflamed tissues of the ureter surrounding a lodged stone. Disposition of the ureteral incision is optional. It may be left open or it may be closed by several interrupted sutures, the results being equally satisfactory. A drain must be placed down to it because there is usually some leakage of urine for several days. When there is much infection above the stone it is better not to suture the ureteral incision because of the benefit derived from free urinary drainage.

Functional Disturbance.—Trattner [29] considered the behavior of the ureter and presented an easily applied method for the recognition of functional ureteral disturbances. The methods of studying ureteral activity may be classified as direct and indirect ocular observation, electrographic and graphic. Studies have also been conducted with the fluoroscope either during or after the injection of opaque solutions, a method which has been subject to criticism.

Trattner's graphic method permits the recording of ureteral activity practically without obstructing urinary escape. The method is adaptable to the intact unexposed ureter of man, as well as to the exposed or excised ureter of an animal, and is of minimal inconvenience to both patient and operator. Ureteral contractions which pass the entire length of the ureter may be classified as complete; those which arise in the renal pelvis but disappear before reaching the bladder, as incomplete, and those which are confined to a small segment of the ureter, as local. The manometer records the complete, as well as many of the incomplete, contractions, and when the latter immediately follow the former the character of the waves is frequently bigeminal or trigeminal. Manometric tracings have been taken in the following conditions: normal ureter; hydro-ureter and hydronephrosis; lithiasis; after ureterolithotomy or the spontaneous passage of ureteral stones; cord bladder; bilateral complete duplication of ureters with simultaneous records of all ureters, and ureteritis of various degrees, tuberculous and nontuberculous.

Manometric tracings are of clinical value in detecting early and late disturbances of ureteral function, in diagnosing dilated ureter and

29. Trattner, H. R.: Ureteral Activity in Some Pathologic Conditions, Arch. Surg. **17**:968 (Dec.) 1928.

pelvis without opaque studies, in deciding into which ureter to inject an opaque solution when various other examinations disclose no difference between the two sides, and in knowing whether the ureter is involved in tuberculosis, calculous disease or tumor. These studies also permit the classification of ureteritis into three groups according to the degree of ureteral activity. Relief of symptoms in patients who have ureteritis or ureteropyelitis appears to occur simultaneously with the recovery of ureteral activity. Aggravation of the disease seems to be concomitant either with hyperactivity or with the loss of peristaltic contractile ability. Trattner stated that the method is not completely efficient in diagnosis, but that it is an additional diagnostic aid.

Elongation.—Vermooten,[30] in carrying out experimental work on ureteral stricture, observed that partial obstruction of the ureter caused its elongation. He attempted to correlate this fact with ureteral kinks and tortuosities as well as with the elongation of the ureter which may be present in ptosed kidneys. In dogs the tortuosity of the ureters was one of the earliest changes noted after the production of a low ureteral stricture. This was associated with so mild a degree of ureteral dilatation that it could be overlooked if it were not compared with the original ureterograms. In view of the large variation in the normal diameter of the ureteral lumen, it is suggested that an indication of elongation of the ureter should mean ureteral obstruction of some kind with slight ureteral dilatation, which is difficult to distinguish from what may be considered the normal limits of the organ.

Ectopia.—Sargent [31] reviewed 186 reported cases of ureteral ectopia: 123 of the patients were females and 63 males. A total of 103 operations was performed on 86 females and 5 males. Nephrectomy was performed in 22 cases; in 11 of these the entire kidney was practically functionless. In 10 cases the kidney had a double pelvis, the lower half draining normally into the bladder and being apparently normal. In the 16 cases in which heminephrectomy was performed, the part of the kidney not removed was noted as sufficiently normal to warrant saving. The clinical picture presented by the 5 men treated surgically was that of disease of the upper urinary tract. Either nephrectomy or heminephrectomy was performed, and all the patients were reported cured. Of the 33 females completing the group in which nephrectomy or heminephrectomy was performed, cure of urinary incontinence was consistently reported. Forty-nine operations of a conservative type were

30. Vermooten, Vincent: The Elongation of the Ureter, J. Urol. **23**:427 (April) 1930.

31. Sargent, J. C.: Ureteral Ectopia, J. Urol. **23**:357 (March) 1930.

performed. Vaginal implantation of the dissected lower end of the ureter into the floor of the bladder was done in 26 cases. Judging the result by the cure of incontinence, 14 operations were reported as successful, and 8 as failures; the result of 4 operations was not noted. Suprapubic implantation of the ureter was performed in 8 cases; in 7 it was successful and in the remaining case the result was not recorded. Two of the suprapubic implantations were done transperitoneally, and 4 extraperitoneally; the method of 2 of the operations was not mentioned. In 12 cases various attempts were made to effect an opening between the ureter and bladder *in situ*.

Nephrectomy, except for its surgical mortality, promises absolute cure in ureteral ectopia and is indicated when the entire kidney is rudimentary or functionless from disease. For male patients especially, the additional removal of the entire ureter, when enormously dilated and tortuous, is advisable. Heminephrectomy is curative, comparatively safe and the procedure of choice when the portion of a double kidney drained by the ectopic ureter is rudimentary or functionless from disease and the remaining part is normal and functionally valuable. Dilatation or infection of the ectopic ureter especially recommends this radical procedure. The value of vaginal implantation of the ectopic ureter into the bladder, although usually curing incontinence, has not been proved so far as the conservation of renal function is concerned. It should be limited to cases in which there is neither dilatation nor infection of the ectopic ureter. Results of vaginal ligation of the ureteral end have not been satisfactory.

[ED. NOTE.—The association of ectopic ureter with disease of the upper urinary tract makes the condition especially amenable to treatment by nephrectomy or heminephrectomy, if the case is suitable. In dealing with the usual infection of the upper urinary tract, ureterectomy is seldom necessary. As was pointed out by Latchem, in exceptional cases a low ureteral obstruction (from calculus or otherwise) with dilatation and suppuration above may create conditions which call for excision of the ureter. Sargent showed that an ectopic ureter is one that frequently needs resection.

Low ureteral ligation, sometimes employed with impunity when tumors of the bladder around the ureteral orifice are resected, cannot often be used in cases of ectopic ureter, because the ureteritis and renal infection above would result in pyoureter and pyonephrosis. For the same reason, reimplantation operations, which all too frequently fail under any conditions, however ideal, are particularly liable to disastrous results if carried out with an ectopic ureter.

Sargent's review brings out well the fact that nephrectomy and heminephrectomy with excision of the ureter are the procedures of choice in dealing with ureteral ectopia.]

Davis [32] stated that ectopic ureter with urethral implantation and without incontinence is rare in the female and presents a difficult diagnostic problem. If the voided urine is purulent, but clear urine is obtained from both ureters and there is no infravesical obstruction or lesion of the bladder to explain the pyuria, ectopic ureter with urethral implantation should always be suspected. The proper treatment is nephrectomy in the case of a single kidney and heminephrectomy in the case of a double kidney, with ureterectomy if the ureter fails to drain well.

Hemorrhage.—Vynalek [33] stated that severe hemorrhage following ureteral meatotomy is rare, but that troublesome bleeding occurs more often than is generally reported. He cited a case in which severe hemorrhage followed the passage of a ureteral calculus with an apparent increase of the sharp splitting of ureteral meatotomy, necessitating suprapubic cystotomy to control hemorrhage. Had it been possible to visualize the point, the bleeding in this case could probably have been controlled through cystoscopic procedures.

Experimental work on dogs showed that severe hemorrhage can occur following ureteral meatotomy. Severe bleeding following meatotomy with scissors should be controlled immediately by high frequency electrodes. Persistent hematuria, even though not marked following any intravesical cystoscopic procedure should, unless contraindicated, be treated by frequent lavage to prevent clotting.

BLADDER

Rupture.—De Tarnowsky [34] reviewed and analyzed all cases of ruptured bladder in Cook County Hospital, Chicago, during the years from 1926 to 1929. To those were added private cases and cases from the Ravenswood Hospital, about fifty in all.

Less than 5 per cent of ruptures of the bladder were caused by or accompanied by fracture of the pelvis. Cystoscopic examination gave negative results if in extraperitoneal rupture the tension of the

32. Davis, D. M.: Urethral Ectopic Ureter in the Female Without Incontinence, J. Urol. **23**:463 (April) 1930.

33. Vynalek, W. J.: Severe Hemorrhage Following Ureteral Meatotomy, J. Urol. **24**:111 (July) 1930.

34. de Tarnowsky, George: Rupture of the Bladder, J. A. M. A. **95**:476 (Aug. 16) 1930.

extravesical fluid equaled that within the bladder, or if the rent in the serosa and muscularis was overlapped by a fold of mucosa.

De Tarnowsky concluded that a large percentage of the accidents reported occurred in cases of overdistended bladders; lying against the anterior abdominal wall, this viscus will burst without any trauma to the bony pelvis. Pain in the lower portion of the abdomen, vesical tenesmus, blood-stained urine or inability to urinate should be sufficient to indicate immediately to the surgeon a probable lesion of the bladder. The average mortality from such lesions, although unquestionably increased by coincident injuries to other organs or tissues, is still too high because primary diagnoses are not being made frequently enough. Rupture of the bladder is as much a surgical emergency as an acute condition in the abdomen, and delay in operating is equally dangerous. Closure of the tear by suture, prevesical or culdesac drainage and catheter à demeure are the three essential operative steps. In individual cases the surgeon may have to modify this technic.

Diverticulum.—Schacht and Crenshaw [35] stated that diverticula are not often found in the bladder of female patients; the ratio of female to male patients is approximately 3:97. In the group of eighteen women with diverticula, thirteen were found to have true diverticula, and five false diverticula. Three patients had urethral caruncle, and one patient a cyst, 1.2 cm. in diameter, at the neck of the bladder. Of the false diverticula, one was the result of injury at childbirth and the other four were the results of operative procedures in the pelvis and abdomen. Symptoms are usually in proportion to the associated infection of the bladder and complications such as vesical calculus or neoplasms of the bladder. Approximately 70 per cent of the women with this condition are between the ages of 35 and 65.

Tumor.—Hamer and Mertz [36] stated that angioma of the bladder is rare. It is probably often a slowly growing, congenital tumor. The patients usually are children and young adults, almost half of the reported cases occurring during the first and second decades of life. Frequently the tumor has a rough surface with bluish-black or violet areas as viewed through the cystoscope, indicating its vascular structure. Fulguration is applicable only to the smaller tumors; surgical removal is possible before the surrounding structures are invaded. If removal is accomplished, cure can be expected.

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35. Schacht, F. W., and Crenshaw, J. L.: Vesical Diverticulum in the Female, J. Urol. **24**:393 (Oct.) 1930.

36. Hamer, H. G., and Mertz, H. O.: Angioma of the Bladder, Surg. Gynec. Obst. **51**:541 (Oct.) 1930.

PROSTATE GLAND

Hypertrophy.—Cabot [37] stated that the most significant conditions leading to death following prostatectomy are renal insufficiency, bleeding, either primary or secondary, and infection. Satisfactory preoperative drainage is the best means of avoiding renal insufficiency. The control of primary hemorrhage or bleeding is satisfactory by either catheterization or suprapubic drainage. In primary prostatectomy the control may be carried out directly under sight, the bleeding points being secured by ligatures or sutures. This is a desirable procedure except that it may require considerable time, and the prolongation of such operations may be inadvisable if the patients are elderly. In two-stage prostatectomy the control of bleeding, preferably by the use of a bag, but also by packing, has become entirely satisfactory and is probably as complete as that obtained by visual control. Neither method appears to have any advantage in secondary bleeding. This form of bleeding occasionally occurs after any method of prostatectomy, and does not appear to depend on the method employed. Following prostatectomy, infection may involve either the wound or the prevesical space or may occur in the region from which the prostate gland has been removed. In regard to infection of the wound and the prevesical space, the two-stage prostatectomy is a distinct advantage over the one-stage. If primary prostatectomy is carried out through an extensive incision, allowing the operation to be done under direct vision, there is more room for infection, more tissues are exposed and, since the operation necessarily is longer, there is greater strain on the resources of the patient and greater opportunity for infection. On the grounds of satisfactory drainage and liability to infection, the two-stage operation is better than the one-stage.

It has been widely believed that functional results following a one-stage prostatectomy carried out under direct vision were likely to be better than those following enucleation. Cabot observed more unsatisfactory results after the one-stage than after the two-stage operation, owing to contraction about the neck of the bladder, resulting in varying grades of stenosis; he expressed the belief that the former method has failed to show better results than the two-stage procedure.

The mortality of prostatectomy is relatively high and can be kept at its lowest level, from 2.5 to 5 per cent, only by taking every precaution. In the long run, the mortality of a properly carried out two-stage prostatectomy is apparently bound to be less than that following

37. Cabot, Hugh: The Place of Two-Stage Prostatectomy in Surgery of the Prostate Gland, Proc. Staff Meet., Mayo Clin. **5**:247 (Sept. 3) 1930.

the one-stage operation. The one-stage operation is more time-consuming and requires greater technical facility, more perfect surgical organization and superior judgment in the selection of cases. To secure the best results, it should be performed chiefly by the surgeons in whose hands perineal prostatectomy is now satisfactory, namely, the experts with large experience.

The requirements for a satisfactory two-stage operation are as follows: The first stage should be carried out in such a way as to avoid opening the prevesical space. The bladder should be opened and explored; the size of the prostate gland and the development of the various lobes should be noted, and the evidence of absence of calculi or diverticula should be confirmed. The drainage tube should be carefully placed in the bladder in such a way as to avoid contact with an enlarged median lobe. The wall of the bladder should be closed tightly about the tube to prevent leakage. The remainder of the wound should be carefully sutured and primary union should be obtained. If the operation is satisfactory, the patient is dry at all times; leakage around the drainage tube points to unsatisfactory technic. If it is possible to carry out the second stage within from seven to ten days, it should be possible to resuture the wound, although somewhat loosely, in such a way that rapid healing takes place; convalescence from the second stage of the operation should not be much longer than that following primary prostatectomy. Cabot concluded that two-stage prostatectomy is in general a safer procedure, that it will not prolong convalescence more than a week or ten days and that this time is well spent in obtaining a lower mortality.

Thomson-Walker [38] stated that the term "fibrous prostate" has crept into surgical nomenclature without careful definition of the type of its pathologic changes. From a series of 185 prostate glands in which full histologic details were obtained, he selected those weighing 20 Gm. or less as representative of glands of this type. After removal, a prostate gland of 18 or 20 Gm. does not appear larger than one would judge the normal gland to be. The author divided clinical forms of malignant growth of the prostate gland into two kinds: primary and secondary. In the primary malignant form, the change is, clinically at least, cancerous from the outset; in the secondary malignant form the gland has at first the character of the ordinary enlarged prostate gland and the malignant changes are engrafted on this. The proportion of primary to secondary malignant lesions of the prostate gland

38. Thomson-Walker, John: Enlarged Prostate and Prostatectomy: II. Selection of Cases of Enlarged Prostate for Operation, Lancet **1**:1219 (June 7) 1930.

is about 1:6. Of 2,496 cases of enlarged prostate gland observed by Thomson-Walker in private practice, the growth was malignant in 247 and a simple enlargement in 2,149. Thus the percentage of malignant growth was 13.5, and that of simple enlargement 86.5. The secondary malignant growth of the prostate gland is engrafted on simple enlargement of the gland. The malignant growth may develop in 1 of 3 situations; it may infiltrate the base of the prostate gland adjacent to the internal meatus and may not be discovered until operation is undertaken; the periphery of the enlarged gland may be affected. In these cases the examining finger recognizes an enlarged gland of elastic consistence. The third area to be affected is where the malignant change has developed in the substance of the enlarged prostate gland. The clinical features are those of simple enlargement of the gland, and at operation the enucleation proceeds smoothly. Attention was first drawn to this type of case by Albarran and Halle, who examined 100 specimens removed as simple enlargement of the prostate gland and found evidence of carcinoma in 14. In 521 cases in Thomson-Walker's private practice, a report obtained on the specimen removed by suprapubic prostatectomy revealed that there were 96 cases (18 per cent) in which areas of carcinoma were discovered. In these cases there was no suspicion of malignancy before operation, and the operation was performed by enucleation under the belief that the prostate gland was the seat of simple enlargement. It was stated that with increasing obstruction of an enlarged prostate gland and accumulation of residual urine, renal function is impaired; the renal insufficiency that results from urinary obstruction is that in which nitrogenous products are excreted in diminished quantity in the urine and accumulate in the blood.

Thomson-Walker concluded from the study of 274 cases that there is no risk of uremia following prostatectomy if the concentration of urea is 2 per cent or more, but that there is a slight risk when the reading is from 1.8 to 2 per cent, and that a single reading of 1.9 per cent is not sufficient to establish the case in this safe zone. There is serious risk when the figure is below 1.8 per cent, and more so when it is below 1.5 per cent. Furthermore, with extreme care it may be possible to operate successfully even when the concentration of urea is below 1.5 per cent. Estimation of the urea content of the blood gives additional information about the functional activity of the kidneys in the excretion of nitrogenous bodies. The normal urea content of the blood is from 20 to 40 mg. per hundred cubic centimeters. MacLean pointed out that these figures are too low in dealing with older men, and that blood urea of from 40 to 50 mg. per hundred cubic centimeters may be

present without indicating serious impairment of renal function. According to Thomson-Walker, sepsis in relation to the enlarged prostate gland and prostatectomy indicates failure of surgical methods. The infection may occur before the operation, it may be introduced at the time of operation or it may occur subsequent to the operation when the cystotomy wound is still open. If the infection is recent and moderate, and there is no evidence of renal involvement, a few weeks' preparation by thorough washing of the bladder and removal of the residual urine, either by intermittent catheterization or by use of the resident catheter, together with diuresis and urinary antiseptics, will suffice as a preparation for the removal of the prostate gland. When a more severe grade of sepsis is present, it will be necessary to perform suprapubic cystotomy and drain the bladder. A large proportion of the patients on whom prostatectomy is performed show signs of arteriosclerosis, a few have valvular disease and some have impairment of the myocardium. The degree of circulatory strain that is permissible in any given case will be decided by the physician and the anesthetist. Some of the patients run grave circulatory risks from the condition of the heart, as well as from the state of the blood pressure. The first point is that many patients submitted to prostatectomy have low blood pressures and a considerable number have very low pressures. Thus, of 107 consecutive patients, 44 (41.1 per cent) had a systolic pressure of 140 mm. of mercury or less, and 19 (17.7 per cent) had a systolic pressure of 120 or less. With very high blood pressure one would expect serious hemorrhage, yet of 15 cases in which the systolic pressure was more than 200, severe postoperative hemorrhage occurred in only 2 (13.3 per cent); in none was the hemorrhage serious at operation. In low-grade pressures of 120 or less, more severe hemorrhage occurred in 4 cases (21.0 per cent) at operation, and in 2 cases (10.5 per cent) after operation. The lower the blood pressure the greater the probability of thrombosis and of pulmonary embolism. In 19 cases in which the blood pressure was 120 or less, there were 3 cases of thrombosis of pelvic or cerebral veins and 2 cases of pulmonary embolism (26.3 per cent); in the remaining 88 cases of the series there were only 2 (2.2 per cent) of thrombosis. In the entire series, only 1 patient died of sudden cardiac failure (systolic pressure, 200). Thomson-Walker's experience made him fear the danger of thrombosis and pulmonary embolism in cases in which the blood pressure is low. Of 16 patients with glycosuria on whom prostatectomy was performed, 12 (75 per cent) recovered from the operation and 4 died (25 per cent); diabetic coma was the cause of death of 2 patients within three days of the operation. Operation was performed on these patients before modern advances in the treatment of diabetes.

Thomson-Walker stated that the best form of treatment for the adenomatous prostate gland is removal by operation unless this is contraindicated. He believed that it has been the experience of all urologists that the operation can be successfully performed on extremely old men. Freyer related that in 1,625 cases of prostatectomy he had operated on 92 patients between the ages of 80 and 90 years, and on 13 in their eightieth year, with 12 deaths (11.5 per cent). This is a fine record of work, but the mortality here is twice that of his total average. In Thomson-Walker's own cases there were 27 patients aged 80 years or more; 3 patients died, a death rate of 11.11 per cent, which closely corresponds to Freyer's figures. Constant skilled attention is necessary in these cases after operation. Another point in favor of early operation is the "silent" prostate gland with chronic urinary retention. This condition is one of the most difficult and dangerous in prostatic surgery. The only way to prevent the development of so grave a complication is thorough examination in all cases of frequent micturition, and continued observation. If residual urine is found, operation should be recommended. Further reasons why operation should not be delayed indefinitely are the danger (1) of sepsis and (2) of malignant changes in a prostate gland which is the seat of simple enlargement.

Thomson-Walker stated that in the ordinary case, the two-stage operation does not appear to be safer than the one-stage operation. Shock is not a factor in uncomplicated one-stage prostatectomy. His experience has been that the second stage of a two-stage prostatectomy is much more likely to produce shock that a single-stage operation. If the open operation is performed when cystotomy has been done previously, it becomes necessary to dissect the whole of the scar tissue and to mobilize the bladder. The procedure is therefore much more serious than a single-stage operation. Hemorrhage is not less in a two-stage than in a one-stage operation. There was no question of sepsis being reduced in the cases commented on, for the bladder was aseptic. In the two-stage prostatectomy, the bladder practically always becomes infected during the period of drainage before prostatectomy. Disadvantages of the two-stage operation are that there are two operations and two anesthetics, and the period during which the patient remains in bed is longer.

Gibson [39] stated that primary closure and healing are applicable to perineal prostatectomy wounds, and can be made the rule rather than the exception. Gauze packs or distensible rubber bags used for hemo-

39. Gibson, T. E.: Primary Closure in Prostatectomy, Ann. Surg. **92**:82 (July) 1930.

static purposes are objectionable for a number of reasons. They stretch the dilated prostatic cavity still farther, which under ideal conditions should be permitted to collapse and shrink as soon as the gland is removed; they cause the patient discomfort, not only by their presence but by their removal, and they delay healing of the wound by leaving a temporary urinary fistula on withdrawal, which ordinarily requires from two to four weeks and perhaps longer to close.

Before primary closure can be done safely, it must be ascertained first that all bleeding has been carefully controlled. If bleeding can be satisfactorily controlled the wound is closed tightly without drainage, and the urinary stream is taken care of by means of a retention catheter through the urethra. If bleeding cannot be checked satisfactorily by suture, the prostatic fossa is packed with strips of gauze.

In perineal prostatectomy it is generally possible to get an adequate view of the neck of the bladder, and in the majority of cases the wound can be closed without using either packs or bags. In a series of twenty consecutive operations for perineal prostatectomy, Gibson was able to do a primary closure successfully in thirteen. In the other seven he felt compelled to resort to packs to check the bleeding completely, thus making primary closure and primary healing impossible. Analyzing the two groups of cases with respect to duration of postoperative convalescence, the average time spent in the hospital by those for whom packs were used was twenty-two days. In the cases of primary closure in which packs were not used, the average time in the hospital after operation was sixteen days.

URETHRA

Calculi.—Debenham [40] reviewed forty cases of urethral calculi recorded at the London Hospital during the last twenty years; impacted calculi occurred in thirty-four male and in three female patients. In the remaining three cases the condition was probably primary urethral calculi. In each instance there was a urethral stricture of long standing, and the symptoms suggested this condition combined with cystitis.

Urethral calculi are referred to as primary or secondary, according to their site of origin. Primary calculi are rare and are formed within the urethra, either behind some obstruction or within the pouch. Secondary calculi are more common; they are formed in the kidney or bladder and are passed down the urethra. The most common site of the calculus is just proximal to the narrowest portions of the urethra. In the normal healthy urethra they are usually impacted either a short distance behind the external urinary meatus or in the prostatic portion

40. Debenham, R. K.: Urethral Calculi, Brit. J. Urol. **2**:113 (June) 1930.

of the urethra just behind the narrow membranous part. Primary and secondary calculi differ in their composition; a primary calculus is phosphatic; a secondary concretion is composed of any or all of the constituents that make up renal or vesical calculi. A primary stone may lie dormant for a long time, the patient having symptoms suggesting urethral stricture or cystitis. The secondary calculus produces sudden obstruction, either complete or partial, and necessitates immediate treatment.

In about half of the men the stone was impacted a short distance behind the urinary meatus. The calculi are usually small and single, rarely multiple, and vary in size from about 1.2 to 0.6 cm. In only one of the thirty-four cases of impacted calculi in men were the stones multiple. If the calculi are of the primary variety, or if they have been lying for a long time in the urethra, for example, those found behind strictures, are more likely to be multiple and larger, as they no longer have to conform to the size of the normal urethra. Multiple stones are also often faceted. Large urethral calculi have not been noted; recently a case was reported of a Chinese boatman who had 2,170 stones weighing 81 Gm. in the urethra.

The symptoms produced by an impacted urethral calculus depend primarily on the extent of obstruction caused by the stone. When complete obstruction results, the typical history is that several hours previously, or perhaps the day before, the patient experiences sudden pain in the penis during urination, associated with sudden cessation in the flow of urine and occasionally followed by the passage of a few drops of blood. Retention of urine follows. When obstruction is partial, the history is often of longer duration, perhaps a day or two, or occasionally two weeks or more. In one case the calculus was impacted in the fossa navicularis of the urethra for twenty-three years. The calculus is often easily palpable in the urethra as a hard lump, especially if the stone is in the penile urethra. Sometimes, if near the external meatus, it may actually be visible. If situated in the prostatic urethra, it may be felt by rectal examination.

In most cases when the stone is situated in the anterior portion of the urethra, it can easily be recovered with forceps. If situated in the posterior urethra, the stone is pushed back into the bladder and then crushed. In some cases external urethrotomy is necessary, and incision is made over the stone, the stone removed and a catheter tied in the urethra for a few days. If the condition is complicated by a stricture of the urethra, dilation, or internal urethrotomy may be performed and forceps used to remove the stone.

Women rarely have urethral calculi, as they do not often have vesical stones and as the urethra is short and dilates readily.

Caruncle.—Olcott [41] stated that the epithelium of caruncles of the female urethra frequently shows enough infolding to make the benign nature appear doubtful to one who is not familiar with this particular structure. Compound acinar glands similar to those described by Skene frequently are present in the female urethra. They were found in seventeen of the twenty-three cases considered. Olcott suggested that these glandular structures may be significant in the formation of caruncles. Twenty-three cases of caruncle were reviewed in which slides were satisfactory and the history fairly complete. The ages of the women varied from 23 to 55 years, the average age being 51. Of the fifteen patients whose marital status was recorded, ten were married and had borne children, three were married but childless, and two were unmarried. Complications noted were: relaxation of the pelvic floor in six patients and probably in several others; hemorrhoids in two, diabetes in one and cystitis in one.

Hermaphrodism.— Kleb's classification of true and false hermaphrodism and his subdivisions are generally accepted. For descriptive purposes the classification developed by Guericolas into glandular and tubular hermaphrodism is most useful, the latter coming under the heading of false hermaphrodism.

McCrea [42] reported a case of the tubular variety; that is, both Müller's and wolffian ducts were present in one person. This case is of additional interest as there was also a neoplasm of the internal genitalia. The patient, aged 31 years, was admitted to the male ward of the hospital in May, 1928, with the complaint of severe pain in the back, obstinate constipation and swelling of the abdomen which was rapidly increasing. Examination revealed a large abdominal tumor, apparently arising from the pelvis, which was about 20 cm. in size. The mass could be felt anteriorly by rectum. Neither testis was present in the scrotum. At operation a large, nodular tumor, partly cystic and partly solid, was found; this rose from the pelvis and was adherent to the rectosigmoid. It was considered that the tumor was malignant, and probably arose from a retained testis. Operation was not possible. On searching for the testes, both were found, but it was noted with some surprise that a tube with a fimbriated extremity lay in

41. Olcott, C. T. Urethral Caruncle in the Female, Surg. Gynec. Obst. **51**:61 (July) 1930.

42. McCrea, E. d'A.: Tubular Hermaphrodite with Teratoma of the Internal Genitalia, Brit. J. Surg. **18**:91 (July) 1930.

relation to each. Complete exploration was impossible. Postmortem examination in July showed marked secondary involvement of the aortic glands and liver. Removal of the pelvic contents revealed: a uterus with broad ligaments and tubes with fimbriated extremities passing to the two gonads previously noted; two vasa deferens passing down the posterolateral margins of the uterus in intimate relation with its wall; two seminal vesicles lying behind and to each side of the lower segment of the uterus, and a well developed prostate gland. The uterine cavity, which showed no evidence of division into uterus and vagina other than narrowing 2.5 cm from its inferior termination, opened into the prostatic urethra at the normal site of the prostatic utricle, and the length of its cavity from urethra to apex was 13.25 cm. The vasa deferens originated from two nodules lying between the layers of the broad ligament situated mesial to the two gonads, but clearly separate from them; they joined the ducts of the seminal vesicles, and the ejaculatory ducts opened at their normal sites on each side of the utricle. The tumor, 20 by 13 by 7 cm., appeared to be a teratoma, and had an attachment to the anterosuperior surface of the uterus and to the anterior aspect of the broad ligament. It had no relation to the two gonads or to the tubes, all of which were free and clearly demonstrated at the operation in May, although at necropsy the appendages of the left side were partially obscured by the tumor and its secondary growths. Microscopic examination revealed that the uterus possessed an apparently normal endometrium and a wall made up of smooth muscle; the tubes, seminal vesicles, vas deferens and prostate gland appeared normal. The gonad of the right side was definitely a testis, and serial section failed to show any trace of ovarian tissue; the left gonad, which was largely destroyed by secondary growths, also proved to be a testis. The tumor contained numerous cysts, the majority of which showed intracystic papillomas; among other tissues found were bone, cartilage, smooth muscle and tubules lined with epithelium. Ectodermal derivatives identified were some rudimentary teeth and a small cyst lined by squamous epithelium from which a few hairs sprang. All the secondary growths examined were papilliferous cystadenomas. It was noted that the patient was typically masculine, without any evidence of female characteristics. A history obtained from his brother and roommate, however disclosed that since the age of 17 there had been attacks of abdominal pain "nearly every month, periodical like a woman," and at such times it was observed that the urine was stained with blood.

UROGRAPHY

Jona and Flecker [43] stated that pyeloscopy is a convenient method for determining the pathologic changes in cases of pain in the kidney when lithiasis is absent. In many cases of pyelitis these investigators have determined by direct observation which drug gives the best contraction of the renal pelvis. Patients who have suffered for years from backache with periodic exacerbations of headache, sweating and rise of temperature, have derived immediate relief from strychnine, physostigmine and morphine, either alone or combined, when citrates and the usually recognized treatments have failed. In cases of hydronephrosis in which the pelvis contracts well and vigorously, the treatment is plication; if the pelvis does not contract and is simply an inert atonic sac, nephrectomy is indicated. In cases in which a malignant lesion occurs early, involving perhaps only a single calix, the absence of contraction of one part of the pelvis associated with "idiopathic" hematuria of renal origin would justify an exploratory operation. In the opinion of Jona and Flecker, too much stress cannot be laid on the necessity for slow injection into the pelvis of the kidney and the danger of rupture occurring if nature's warning of pain is ignored.

Iopax.—Braasch [44] stated that from the experience of those who have employed iopax its greatest value probably will be in determining the condition of the kidneys in cases in which ureteral catheterization is difficult or impossible. This would include cases of intolerance, a contracted and tuberculous bladder, anatomic obstruction of the ureter, extensive vesical neoplasm, prostatic obstruction, impassable stricture of the urethra, rectal implantation of the uterus and, in infants and older patients, cases in which introduction of the cystoscope is difficult because of deformities. The intravenous method permits bilateral pyelography without the dangers accompanying bilateral retrograde pyelography; this should be of particular value in the presence of polycystic kidney, bilateral hydronephrosis and fused and solitary kidney. It will also be helpful to the lists of tests of differential renal function, which frequently have left doubt as to the functional capacity of the kidney under investigation. Iopax offers a better medium for retrograde pyelograms than sodium iodide, since it has none of the irritating qualities of the latter, and since, because of the large content of iodine, it casts a dense shadow.

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43. Jona, J. L., and Flecker, H.: Pyeloscopy: Radioscopy of the Kidney Pelvis, Surg. Gynec. Obst. **51**:50 (July) 1930.

44. Braasch, W. F.: Intravenous Urography, editorial, Surg. Gynec. Obst. **51**:421 (Sept.) 1930.

Although the method of intravenous urography is available to the general practitioner, interpretation of the urogram frequently is difficult and should be referred to those who have had extensive experience. In some cases the use of iopax may render cystoscopic examination unnecessary, but its interpretation will often have to be accompanied by cystoscopic data in order to complete the diagnosis.

Galbraith and Mackey [45] stated that iopax contains 42 per cent of iodine by weight and is possessed of a high degree of radiopacity. The original clinical investigations were carried out by von Lichtenberg and Swick. This drug, injected intravenously in solution, is rapidly excreted by the kidneys almost in its entirety. Roentgenograms taken during excretion of the drug give satisfactory visualization of the urinary tract. In a preliminary series of experiments on animals with iopax, Galbraith and Mackey's object was to determine whether or not this drug was capable of injuring the renal parenchyma. For this purpose they employed rabbits and administered the standard dose for man for each kilogram of body weight, and a series of larger doses up to seven and a half times the standard amount. Fairly satisfactory visualization of the urinary tract was obtained by the standard dose, and it is noteworthy that improvement in the roentgenographic pictures did not follow the use of larger doses. It is Galbraith's and Mackey's belief that the sharp demonstration of the renal parenchyma may prove a valuable feature of the method in human beings. A toxic effect was not produced in any animal, even with the larger doses. Microscopic examination of the kidneys failed to reveal evidence of injury to the renal parenchyma, either immediately after the excretion of iopax or at intervals up to forty days after treatment.

Galbraith and Mackey concluded that iopax is practically harmless, and is unlikely to produce injury when used in doses sufficient to give satisfactory roentgenographic pictures.

Urethrography.—Knutsson,[46] after briefly reviewing the method used in urography, described a clamp for the penis made for that particular purpose. The clamp makes the examination simpler and more convenient. He also commented on the so-called collicular elongation of the posterior urethra. In contradiction with Dressler, he holds that only from 1 to 2 cm. of the shadow above the colliculus seminalis is caused by the urethra and that the remaining part of it is caused by some of the opaque fluid collecting in a fold of mucous membrane at the bottom of

45. Galbraith, W. W., and Mackey, W. A.: Uroselectan: A Preliminary Experimental Note, Brit. J. Urol. **2**:122 (June) 1930.

46. Knutsson, Folke: On the Technique of Urethrography, Acta radiol. **10**: 437, 1929.

the bladder. The elongation of the urethra is thus only apparent, and it is not of significance in estimating the size of the prostate gland.

INFECTION OF THE URINARY TRACT

Von Lichtenberg [47] considered the juncture of the urinary and genital tracts a potential source for the spread of disease. The intimate topographic contact with a common blood, lymph and nerve supply makes it seem inevitable that a pathologic process in one of the tracts will also affect the other. A primary, exogenous infection of the prostate gland and seminal vesicles will be the etiologic factor for secondary pathologic changes in the upper part of the urinary tract. A number of cases of ureteral stricture, ureteral kinks, periureteritis, perinephritis and pyogenic renal disease are caused by diseases of the adnexa.

A point of view of pathologic change in the system leads to a correct diagnosis in such cases and forms the background for proper treatment. It allows the correct pathologic evaluation of ureteral disease. By this means von Lichtenberg found the connecting link which joins the diseases of the lower urinary tract and genital organs with those of the kidney into one pathologic and clinical unit.

Von Lichtenberg divided the cases into two large groups: those in which cure can be effected by conservative treatment of the adnexa, and those in which a surgical procedure is necessary to produce healing. Except in cases in which the disease of the vesical sphincter is already the cause of residual urine, operation is performed only after conservative treatment has been unsuccessful.

Conservative treatment consists of diathermy of the adnexa, injections of sulphonated bitumen, N. F., sitz-baths and intravenous injections of sodium iodide, acriflavine, mercurochrome-220 soluble, arsphenamine and methenamine. Von Lichtenberg has seen good results after the long-continued use of hexylresorcinol with diathermy. It seems to have a favorable influence on postgonorrheal infections of the adnexa.

[Ed. Note.—It is remarkable that in the past so little emphasis was placed on the causal relationship between genito-urinary and adnexal diseases. Recent American literature on the subject is especially scanty. Urologists in this country have, as pointed out by Braasch, paid more attention to distant foci of infection. For this reason, von Lichtenberg's article presents a point of view that will doubtless arouse much interest and comment. Hunner has often emphasized the relationship of endocervicitis, adnexal inflammation and even normal pregnancy to the

47. von Lichtenberg, A.: Kidney and Ureteral Lesions Secondary to Adnexal Disease, J. Urol. **24**:1 (July) 1930.

development of ureteral stricture and stasis of the urinary tract. Von Lichtenberg, while avoiding this subject, brings out ideas of the same general order. The urologist must study his male patients carefully from the standpoint of related prostatic or seminal vesical disease; in a study of women the intimate cooperation of the gynecologist must be sought if the urologist is not also a gynecologist. Operative measures are to be reserved for those cases which do not respond to more conservative types of treatment, such as outlined by von Lichtenberg.]

Keyes [48] stated that because genital infections are often old and almost forgotten by the patient, they are easily overlooked when urinary trouble arises. Contact of the seminal vesicle with the ureter is of great interest in cases of ureteral stricture and renal infection.

Braasch [49] observed that, in looking for foci of infection with chronic urinary infections, American urologists have paid more attention to tonsils and to teeth than to the adnexa. Many have recognized these adnexal infections and treated them, as well as other foci, by both conservative and radical methods, without reducing the degree of infection in the kidneys. Von Lichtenberg has not only removed foci, but has attempted to overcome any possible interference in renal drainage. He frees the ureter from both periureteral and intra-ureteral obstructions. He also frees the kidney from adhesions and performs nephropexy, believing that the renal position or pararenal obstructions may interfere with urinary drainage. He drains the kidney by putting a catheter through the cortex by his own method.

In reviewing 1,200 cases of chronic infections of the kidney, Braasch found that nature aids in remedying these conditions. Of the various methods employed, no single procedure could be regarded as a panacea. At the end of five years a third of the patients were free from symptoms, apparently largely spontaneously, although they had undergone every form of treatment. A considerable percentage of the remaining two-thirds should be benefited by the treatment outlined by von Lichtenberg. One of the urologic problems that remains to be solved is the discovery of some method, either by vaccine or intravenous medication, to overcome chronic infections in the kidney which do not respond to various forms of treatment now employed.

In women, chronic pyelonephritis occurs in less than 40 per cent, whereas acute pyelonephritis occurs in approximately 80 per cent. A careful search should be made for pelvic infection, and, if present, it should be removed. The cervix should be examined carefully as a possible

48. Keyes, E. L., in discussion of von Lichtenberg (footnote 47).

49. Braasch, W. F., in discussion of von Lichtenberg (footnote 47).

focus of infection, and cultures are frequently indicated. In many cases, amputation of the cervix was indicated, and in some cases this procedure was followed by excellent results.

Oeconomos [50] stated that infection of the urinary tract by colon bacillus is of significance because of its frequency, manifold clinical forms, complications, sometimes difficult diagnosis and the numerous and new treatments. In certain circumstances toxins are secreted, the intestinal epithelium is altered, and the colon bacillus enters the blood; it may determine septicemia, in the course of which the organism can be localized as a result of urinary stasis in the kidneys, ureters, bladder, prostate gland, seminal vesicles and urethra, thus manifesting the complete range of the urinary infections.

The origin of such a condition is often an infection of the intestines, especially fecal stasis and the presence of intestinal parasites. Fecal stasis brings about erosions or intestinal changes that allow the colon bacillus to filter through the intestinal walls, producing autointoxication. Urinary stasis is the prime factor in localizing this infection through the urinary organs. From the experimental point of view, the colon bacillus acts by means of its toxins, which are more dangerous as they become older. This bacillus often follows the hematogenous route through two stages; it first enters the lymphatic vessels and finally pours into the general circulation.

The treatment of infection of the urinary tract by the colon bacillus must be directed to stasis, the infection, and the initial lesion giving rise to the infection. Stasis should be controlled by the proper methods and the infection by the serum anticolon bacillus of Vincent. If stasis is not apparent, treatment should be directed toward the intestines by diet, administration of liquid petrolatum, lavage, etc.; with regard to the urinary tract, collargol should be given by mouth, alternating with phenyl salicylate, associated with methylene blue (methylthionine chloride, U. S. P.) and the tract should be lavaged; the infection should be attacked by the anti-*Bacillus coli* serum of Vincent.

Bacteriophagy.—Krueger, Faber and Schultz [51] stated that data obtained by periodic examinations of specimens of urine from eight cases of acute urinary infection, in which alkalis were given by mouth, indicate that alkalization, when effective, may facilitate an increase of the virulence of bacteriophages naturally occurring in the urine, probably by providing the optimal reaction for bacteriophagy. In twelve cases of acute

50. Oeconomos, Spyridion: Bacillus Coli Infection of the Urinary Apparatus, Brit. J. Urol. **2**:141 (June) 1930.

51. Krueger, A. P.; Faber, H. K., and Schultz, E. W.: Observations on the Bacteriophage in Infections of the Urinary Tract, J. Urol. **23**:397 (April) 1930.

infection of the urinary tract, a strain of colon bacillus resistant to the bacteriophages was harbored in one (8 per cent), whereas in seventy-seven cases of chronic infection of the urinary tract, forty-two patients (54 per cent) were infected with organisms resistant to bacteriophages. In thirty-five cases of chronic conditions, bacteria were harbored that were capable of complete lysis by one or more races of bacteriophages. In only three of sixteen cases in which pooled suspensions were given was prompt recovery noted; two patients failed to respond to the treatment, and eleven gradually recovered. Of nineteen patients to whom matched individual races of bacteriophages were administered, only one recovered promptly, four failed to recover and fourteen recovered gradually. Twenty-five of thirty-five patients recovered gradually; their recovery was not definitely attributable to the bacteriophages. Four patients recovered rapidly, and six failed to recover.

The general trend of the results does not make it possible to state with accuracy how much value may be attributable to the bacteriophage as a therapeutic agent in chronic urinary infection. The limited number of cases would preclude any far-reaching conclusions. In the experience of these investigators the bacteriophage treatment for urinary infection has failed to realize the good results reported by previous investigators.

Martin [52] expressed the opinion that to obtain restoration to normal of diseased urinary organs, it is necessary to reestablish the free flow of urine, to eradicate the origin of disease, to collaborate with nature and to seek the help of an antiseptic, if there is one for the germ in question.

Jaeggy [53] emphasized the necessity of taking into account the manner of urinary infections and at the same time of treating the primary source, if possible. The true urinary acidity should be found and controlled daily during treatment. A simple and rapid method of determining the true urinary acidity was described. For practical purposes it is well to distinguish strong or weak alkalinity, and strong, medium or weak acidity. From the evidence of numerous works on the subject, the value of urinary antiseptics hardly agrees with their bacteriologic power in vitro. The greater part of such preparations react sooner in a medium as stimulants to means of defense rather than as bactericides. The old preparations of phenyl salicylate, methenamine, camphoric acid and the balsams continue to retain the positions acquired, and have hardly been supplanted by new preparations. Among the latter, the arsenobenzols, owing to their almost specific action

52. Martin, A. P.: Urinary Antiseptics, Brit. J. Urol. **2**:139 (June) 1930.
53. Jaeggy, E.: Urinary Antiseptics, Brit. J. Urol. **2**:140 (June) 1930.

against staphylococci, have shown value as a therapeutic measure. Mercurochrome-220 soluble should be reserved for conditions that have resisted milder remedies.

CHYLURIA

Kidd[54] described two cases of chyluria and filariasis in which surgical treatment was given. One patient who had been treated for infection of the urinary tract later passed large quantities of milklike urine. A catheterized specimen looked like milk, and microscopically it contained large numbers of minute fat droplets; there were traces of pus and bacilli. Specimens taken from the right kidney on two separate occasions contained fat; the urine from the left kidney was normal. A roentgenogram was negative for stone, but pyelograms showed a dilated hydronephrotic right kidney. Filarial embryos could not be found in the blood or the urine. Abdominal nephrectomy was performed. The rectus muscle was turned inward, and the peritoneal cavity was opened and explored; evidences of dilated abdominal lymphatic glands, however, could not be detected. The right kidney was exposed by cutting the peritoneum outside the ascending colon. The right ureter at the ureteropelvic juncture formed an S-shaped kink with high valvular insertion of the ureters into the pelvis. The pelvis appeared as a distended cyst, and the renal substance was lobulated and thinned to less than a third of its usual thickness. The blood supply was normal. The kidney was hardened in formaldehyde and then opened and dissected. Evidence of the presence of filarial worms or embryos could not be found. The appearance was that of infection and hydronephrosis. Convalescence was uneventful.

In a number of cases of chyluria reported in recent years, ureteral catheterization showed that the disease was confined to one kidney. In many cases the symptoms were not severe enough to warrant operative procedure; only six are reported in the literature in which operation was performed, and in only three cases was it successful. Kidd found it necessary to operate in the first case on account of the presence of congenital hydronephrosis. In the second case, that of a youth, aged 19, the left testis was greatly enlarged, pear-shaped, elastic and tense; it could not be determined whether the swelling was fluid or solid. An exploratory operation was performed, the testis being exposed through a long incision extending from over the cord, the full length of the scrotum. The tunica vaginalis, tensely distended with nontranslucent fluid, was incised and a large quantity of fluid resembling milk

54. Kidd, Frank: Surgical Treatment of Chyluria and Filariasis, Brit. J. Urol. **2**:15 (March) 1930.

escaped. Examination of the cord revealed a number of tortuous dilated lymph vessels filled with clear translucent fluid. The majority of these lymphatic glands were cut across, allowing the fluid to escape. On further examination the fluid was found to contain embryos of *Filaria sanguinis-hominis* in an active state but no trace of fat. The hydrocele sac was removed, and the major portion of the skin was stitched up, provision being made for adequate drainage of the fluid. Recovery was uneventful. Fluid continued to escape from the wound for about three weeks, after which the wound became dry and healed soundly. The left testis, when examined eight months later, appeared to be normal. This case suggests the following surgical principle in dealing with filariasis: When an exposed organ is found to present a large number of varicose lymphatic glands distended with clear, milky or pink fluid, the condition is probably due to filariasis, and it may be worth while to cut across the main mass of dilated lymphatic glands and arrange for suitable drainage to the surface of the skin.

From a review of the literature the prognosis of chyluria seems to be unfavorable. In the presence of renal or vesical colic, large doses of sodium citrate prevent coagulation of the fibrin, with relief of the symptoms. Secondary infections of the kidneys and bladder should be treated by renal and vesical lavage and by urinary antiseptics. Arsphenamine or neoarsphenamine may sometimes exert a lethal effect on the parasites, and should be tried in all cases before surgical intervention. Intravenous injections of tartar emetic have also produced good results, and may be tried if arsphenamine fails. Kidd expressed the belief that if chyluria is unilateral, if drugs fail to cure it and if the patient is losing weight or suffering from painful symptoms, nephrectomy is apparently justifiable and may bring about a cure. In cases of bilateral renal chyluria, if there are dangerous complications, exposure of each kidney and upper end of the ureter from behind the peritoneum by two separate incisions, with incision of the lymph varices if found and provision for their drainage to the skin, may prove beneficial. A successful surgical attack has been made on vesical chyluria. Bloch, in 1913, cured such a condition by destroying with the cautery snare a burst lymph varix which he could see in the wall of the bladder.

DYSFUNCTION OF THE NERVE

Mertz and Smith[55] reviewed thirty-nine cases of dysfunction of the nerves of the urinary tract, thirteen of which were their own. In

55. Mertz, H. O., and Smith, L. A.: Posterior Spinal Fusion Defects and Nerve Dysfunction of the Urinary Tract, J. Urol. **24**:41 (July) 1930.

six of the twenty-six cases reviewed from the literature, observations made at necropsy were given. In thirty-four cases the complaint was urinary incontinence, associated with retention of urine in fifteen. Retention of urine without incontinence occurred in three cases. In eleven cases the retention was associated with urinary reflux and dilated ureters and pelves, while in one case there was retention of badly infected urine without urinary reflux or ureteral changes. Coexisting neurotrophic changes involved the renal sphincter in eleven cases, and the lower extremities in eleven cases. Disturbed sensation of the legs or about the vulva or anus was noted in four cases. Unusual conditions of the skin over the lumbosacral region, such as hypertrichosis, discoloration, tumor, dimpling and postoperative scar, were present in eight cases. In two cases, no evidence of paresthesia or trophic changes in the extremities was found at operation. Operation was performed in twenty-one cases reviewed from the literature; in two cases which Mertz and Smith had observed, operation benefited one patient and cured the other. Observations at operation and the clinical results following operation indicated nerve dysfunction. Roentgenograms of the lumbosacral region in thirty-three cases showed varying degrees of anomaly of spinal fusion. In nine cases injection of iodized poppy seed oil 40 per cent was made into the subarachnoid space; seven cases showed definite evidences of local pressure on the nerve structures; in one case the observations were indefinite, and in one they were misleading.

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